Clinical Development of the First Bioreactor-generated Pediatric Inactivated Enterovirus A71 Vaccine

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The Need of an Enterovirus 71 Vaccine

- EV71-associated HFMD/Herpangina in young children have a high risk for severe neurological complications, or death

Major EV71 outbreaks in Asia-pacific regions

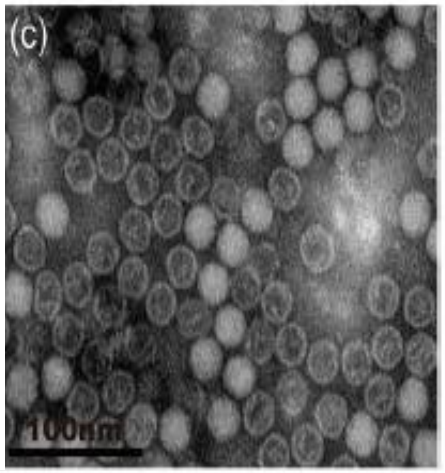
Country	Year	HFMD/ Herpangina cases	Severe cases	Death
Taiwan	1998	129,101	405	78
	2008	-	346	14
China	2008	488,955	1,165	126
	2009	-	10,509	353
	2010	-	-	905
	2011	-	-	230
Vietnam	2011-2012	200,000	-	207
Malaysia	2006	-	436	6
Singapore	2000-2001	-	-	8
Korea	2009	-	92	2

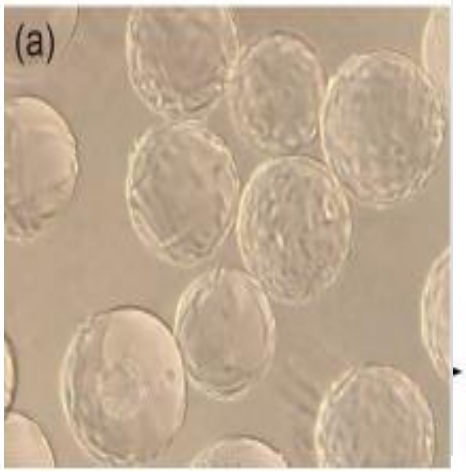
- Mortality rate～10-25%
- Increasing HFMD outbreaks happened in Asia-pacific region since late 1990s.
- Annual HFMD cases: 90,000-140,000 (Taiwan), >0.5-1.2 millions (China)
- **No antiviral or vaccine for Taiwan or Asia-pacific region**

Yip, et al Emerg Health Threats, 2013, 6:19780
M.S. Lee, PLoS Negl Trop Disease, 2012
E.J. Yi, Clin Exp Vaccine Res, 2017

Facts sheet of Enterovax for EV71 Prevention

- EV71 E59 strain (B4), formalin-inactivated, alum-adjuvanted, whole virus particles
- Vero cells with micro-carrier system, serum-free
- Scalable single-use bioreactor (50L & 200L), robust process
- Highly purified
- PFS (pre-fill syringe) for single use
- PIC/S GMP certified



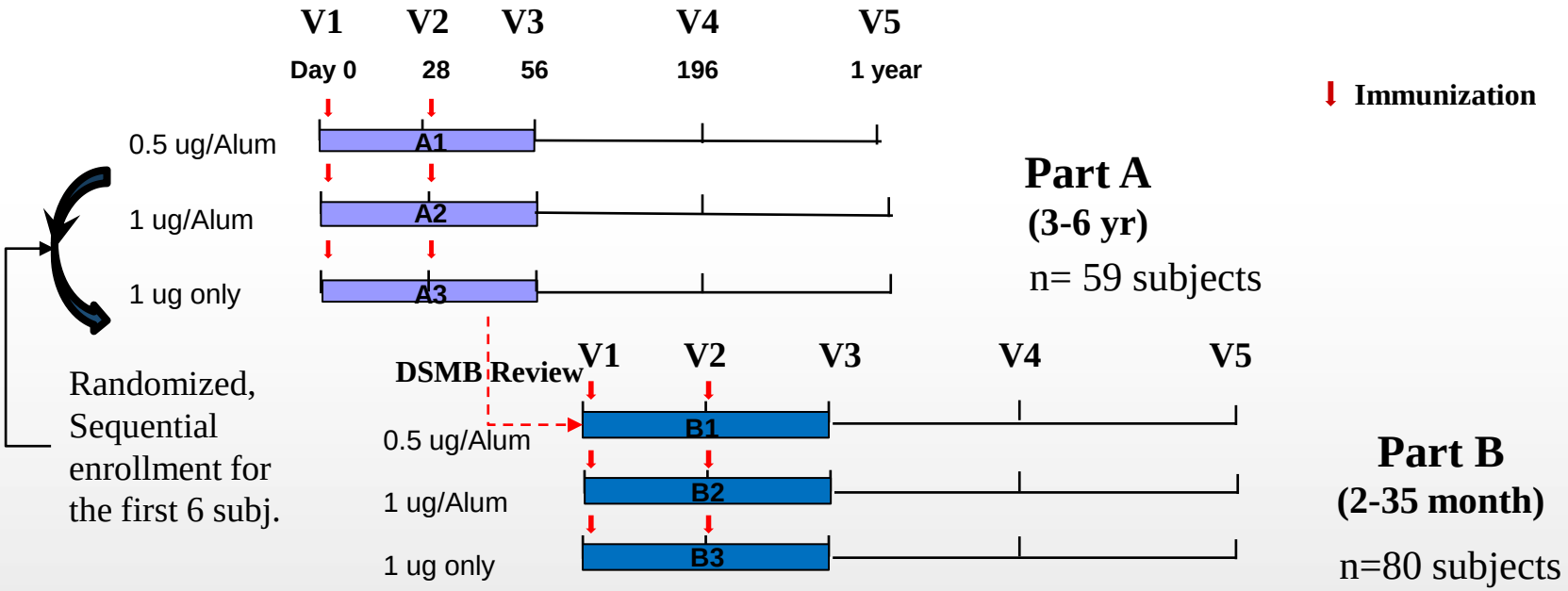


Clinical Studies Conducted

Study	Subjects/Age	Dose group	Regimen	Endpoints	Clinical trials.gov ID
Ph 1 (2011-2012)	60 healthy adults/ 20-<60 yr old	10ug, 5 ug/Alum	2 doses, 21 days apart	Safety and Immunogenicity	NCT01268787
Ph 2a (2015-2016)	122 subjects/ 6 month-6 yr old	0.5, 1, 2 ug/Alum, and 2 ug without Alum	2 doses, 28 days apart	Safety and Immunogenicity	NCT02777411
Ph 2b (2016-2017)	139 subjects/ 2 month-6 yr old	0.5, 1 ug/Alum, and 1 ug without Alum	2 doses, 28 days apart	Safety, Immunogenicity, Immune Persistency	NCT03268083

- Due to process expansion to the single-use bioreactor, a bridging Ph2 study (Ph2b) was conducted
- Immunogenicity: **GMT, SCR** determined by the EV71-specific neutralizing Ab titer

BR (Bioreactor)-EV71 Ph2 Study Design

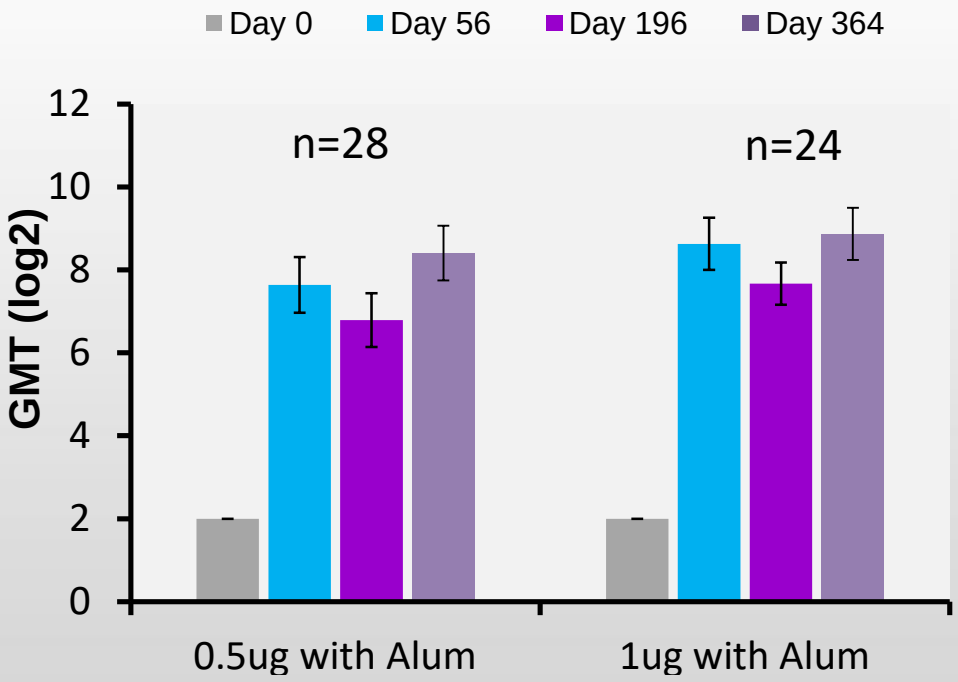


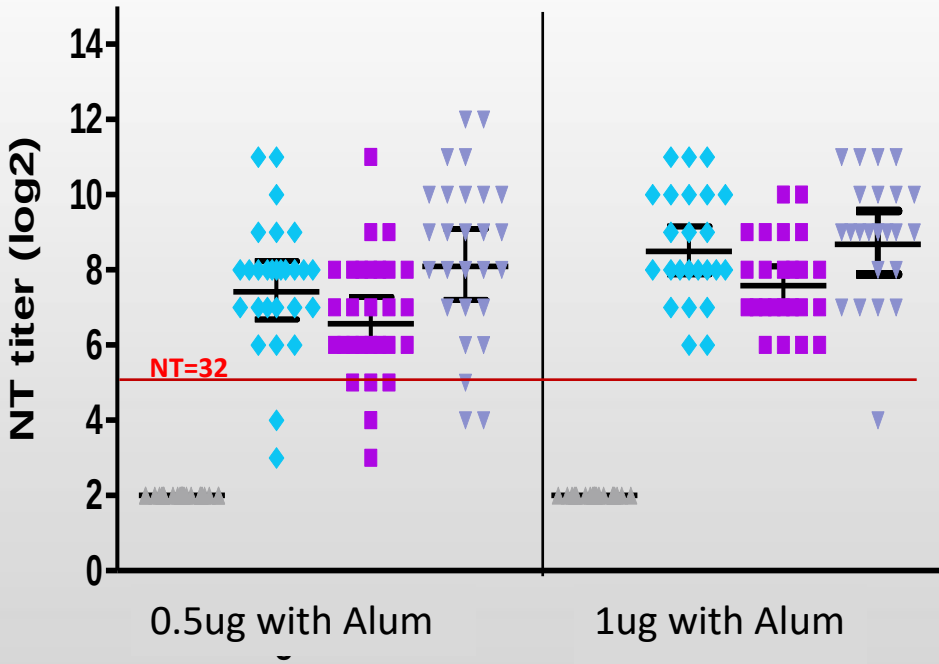
- 3 dosages: 0.5, 1 ug/Alum and 1 ug/without Alum
- 2 i.m. injections each with 28 days apart
- Sequential immunization for the first 6 subjects
- De-escalated vaccination from the elder to the younger children
- DSMB 14 days after 2 injections for partA
- Endpoints: Safety & Immunogenicity (NT titers)
- Immune persistence up to 1 year
- 139 subjects

0.5 ug/dose Induces Sufficient GMT

- **GMT** peaked on Day 56 and decreased about 50% on Day 196, and maintained or slightly increased after Day 364
- **SCR**[1] remained at >90% for 0.5ug/Alum, and 100% for 1 ug/Alum on Day 364

[1]SCR: NT≥32 for naïve or 4-fold increase for non-naïve





Naïve subjects (2-35 month old)

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Enterovax induces cross-NT Ab against C4 & B5

	B4	C4a (TW)	C4a (CH)	B5(TW)
Ph2a-seronegatives (random, n=16)				
Day 56	378.1	145.8	64.0	103.2
NT≧32	100%	100%	94%	100%
Ph2b-seronegative (1 ug/Alum, n=20)				
Day 56	374.8	194	111.4	(in testing)
NT≧32	100%	100%	95%	

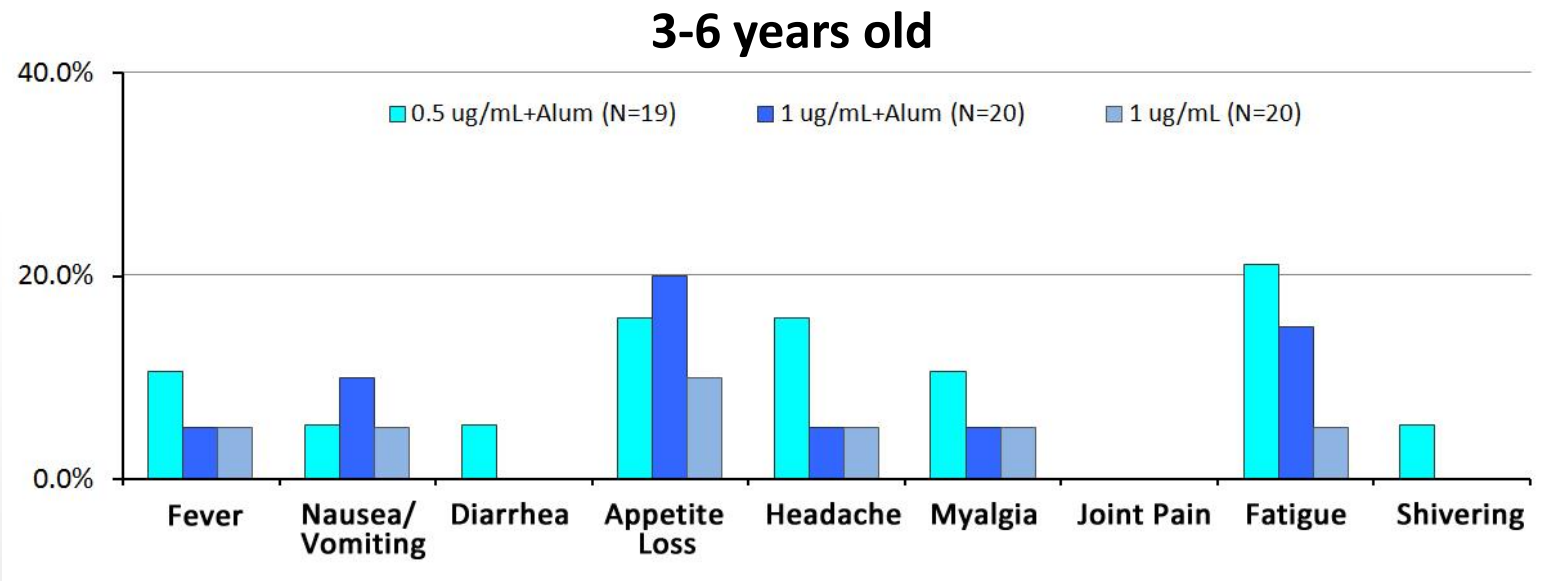
- Data from a smaller subset suggested Enterovax can also neutralize C4 and B5 isolates from Vietnam

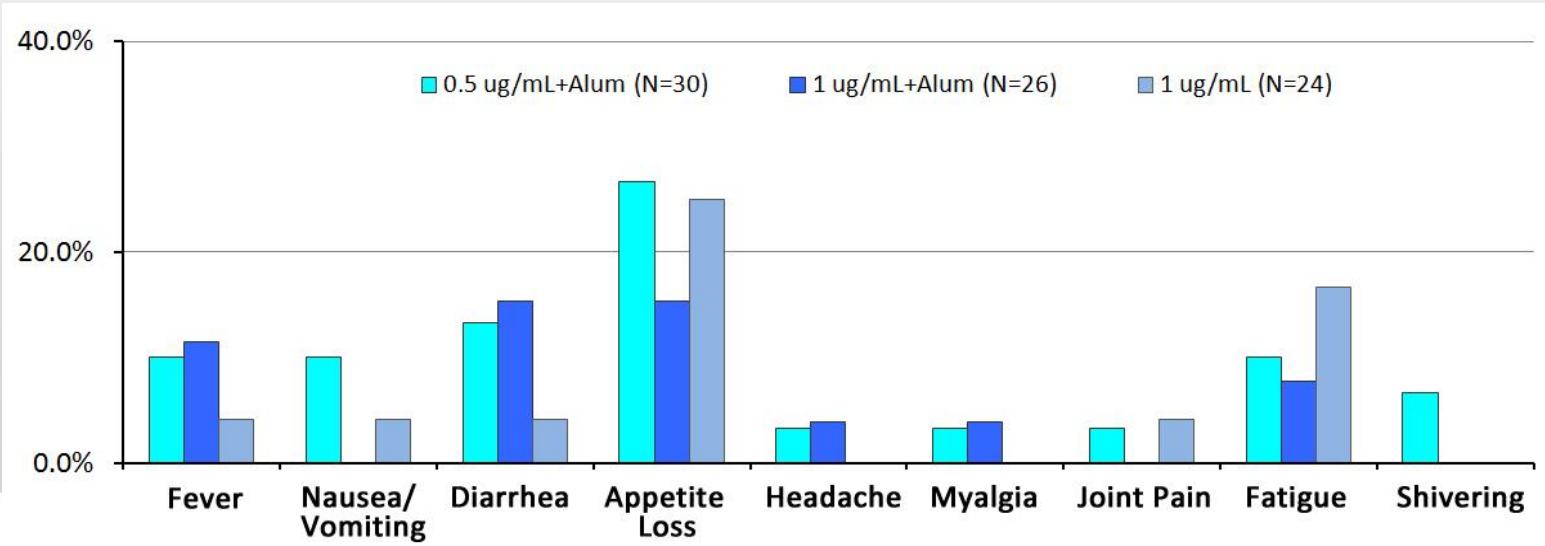
Solicited Local AE by Vaccination

Top 3 AE

	Aged 3 to 6 years old				*Aged 2 to 35 months old*			
	Group A1 ***0.5µg TP+ adjuvant***	*Group A2* ***1.0µg TP+ adjuvant***	*Group A3* ***1.0µg TP***	*p-value*	*Group B1* ***0.5µg TP+ adjuvant***	*Group B2* ***1.0µg TP+ adjuvant***	*Group B3* ***1.0µg TP***	*p-value*
FIRST Vaccination	N = 19	N = 20	N = 20		N = 30	N = 26	N = 24	
Any local event	9 (47.4%)	8 (40.0%)	5 (25.0%)	0.3531	8 (26.7%)	10 (38.5%)	4 (16.7%)	0.2622
Pain	6 (31.6%)	7 (35.0%)	4 (20.0%)	0.5912	6 (20.0%)	3 (11.5%)	3 (12.5%)	0.7303
Tenderness	8 (42.1%)	7 (35.0%)	5 (25.0%)	0.5462	5 (16.7%)	3 (11.5%)	1 (4.2%)	0.4065
Redness	2 (10.5%)	3 (15.0%)	1 (5.0%)	0.6803	4 (13.3%)	8 (30.8%)	1 (4.2%)	0.0430
Swelling	0 (0.0%)	2 (10.0%)	1 (5.0%)	0.7662	4 (13.3%)	5 (19.2%)	0 (0.0%)	0.0780
Ecchymosis	1 (5.3%)	0 (0.0%)	1 (5.0%)	0.7662	1 (3.3%)	2 (7.7%)	2 (8.3%)	0.7290
SECOND Vaccination	N = 18	N = 20	N = 20		N = 30	N = 24	N = 23	
Any local event	8 (44.4%)	8 (40.0%)	3 (15.0%)	0.1140	5 (16.7%)	5 (20.8%)	7 (30.4%)	0.5104
Pain	6 (33.3%)	8 (40.0%)	1 (5.0%)	0.0215	3 (10.0%)	1 (4.2%)	5 (21.7%)	0.1692
Tenderness	5 (27.8%)	5 (25.0%)	1 (5.0%)	0.1462	3 (10.0%)	2 (8.3%)	3 (13.0%)	0.9012
Redness	4 (22.2%)	2 (10.0%)	1 (5.0%)	0.2712	3 (10.0%)	3 (12.5%)	2 (8.7%)	1.0000
Swelling	2 (11.1%)	2 (10.0%)	1 (5.0%)	0.8582	3 (10.0%)	1 (4.2%)	2 (8.7%)	0.7632
Ecchymosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	--	1 (3.3%)	1 (4.2%)	3 (13.0%)	0.4364
ANY Vaccination	N = 19	N = 20	N = 20		N = 30	N = 26	N = 24	
Any local event	11 (57.9%)	9 (45.0%)	7 (35.0%)	0.3902	10 (33.3%)	10 (38.5%)	7 (29.2%)	0.7616
Pain	9 (47.4%)	9 (45.0%)	4 (20.0%)	0.1540	7 (23.3%)	4 (15.4%)	5 (20.8%)	0.7800
Tenderness	8 (42.1%)	8 (40.0%)	5 (25.0%)	0.4953	6 (20.0%)	5 (19.2%)	3 (12.5%)	0.8114
Redness	4 (21.1%)	3 (15.0%)	2 (10.0%)	0.6075	4 (13.3%)	8 (30.8%)	3 (12.5%)	0.1870
Swelling	2 (10.5%)	2 (10.0%)	2 (10.0%)	1.0000	5 (16.7%)	5 (19.2%)	2 (8.3%)	0.5810
Ecchymosis	1 (5.3%)	0 (0.0%)	1 (5.0%)	0.7662	2 (6.7%)	2 (7.7%)	4 (16.7%)	0.5227

Summary of Systemic AE by any vaccination

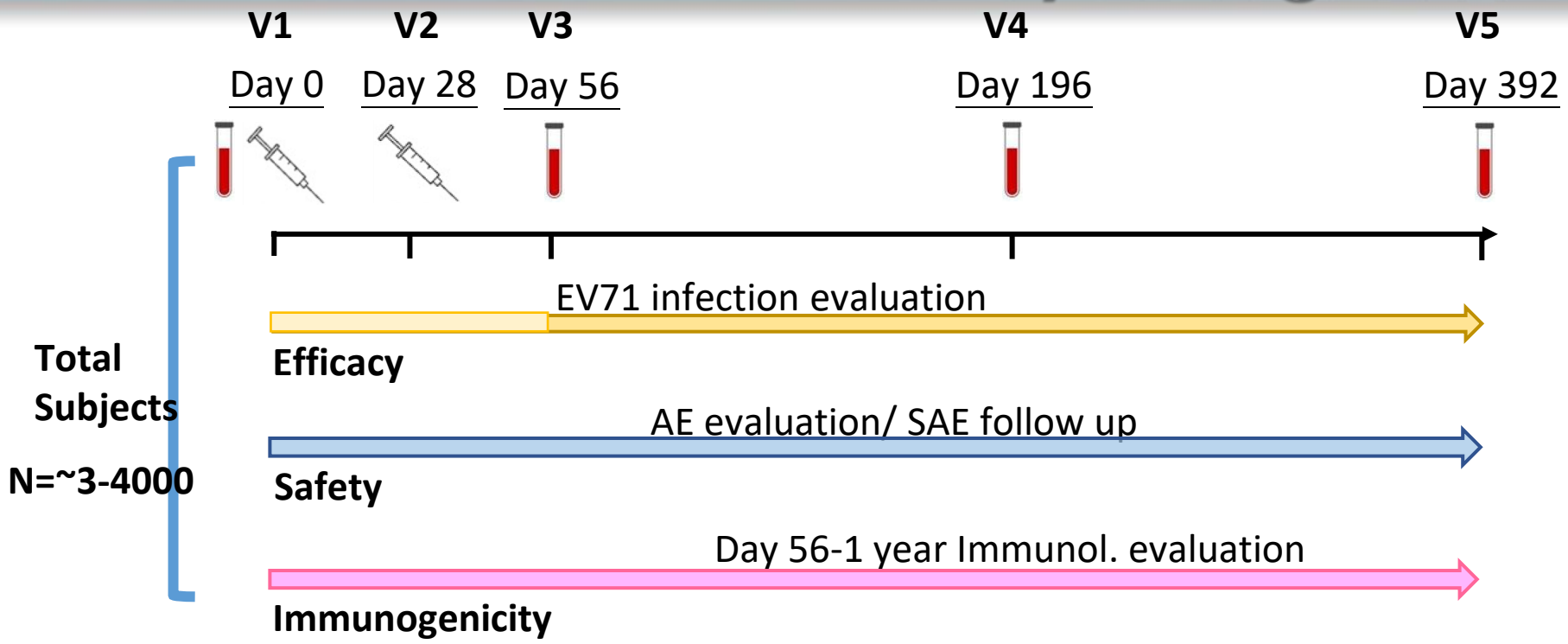




Summary of BR-EV71 B4 Phase II Study Results

- ✓ After 2 vaccinations with 0.5 ug or 1 ug/Alum, EV71-B4 vaccine can induce sufficient GMT and SCR, which peaked on Day 56
  - GMT at Day 56: 220-390
  - SCR at Day 56: > 90%
- ✓ With 1 ug/Alum per dose, GMT titer persists at sufficient level after 1 year, and the SCR is maintained at 100%
- ✓ EV71-B4 vaccination can induce cross-NT Ab against C4 & B5 isolates from Taiwan & China
- ✓ EV71-B4 vaccination appears to be tolerable for 2 months to 6 years old children

Phase 3 Pivotal Study Design



Multicentered, double-blinded, placebo controlled
2 months to 6 yr old
1 ug/0.5 mL per dose

Primary endpoints:
Efficacy
Immunogenicity/SPR

Secondary endpoints:
Safety
Immunogenicity/GMT, SCR,
Immune persistence
Lot consistency
Cross-neutralization

Enterovax Conclusions

- ✓ The 1st EV71 vaccine generated using the state-of-art Bioreactor technology with robust process and better quality
- ✓ Immunogenic and Safe; can cross-neutralize C4 & B5 subgenotypes
- ✓ Pivotal Phase 3 to be started in 2018 Q2

Thank you for your attentions!

Enimmune Corporation, Taiwan

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