Immunogenicity of Takeda's Bivalent Virus-like particle (VLP) Norovirus Vaccine (NoV) candidate in Children from 6 months up to 4 years of Age

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ABSTRACT

Background: With introduction of routine childhood rotavirus vaccination, norovirus is now the major cause of medically-attended gastroenteritis in children. Takeda is developing NoV that contains genotypes GI.1 and GII.4 consensus (GII.4c) sequence VLPs. We report the immunogenicity data of NoV administered to children from 6 months up to 4 years of age.

Methods: Two age cohorts (1 to < 4 years, and 6 to < 12 months, n = 120 per cohort) were enrolled in this ongoing double-blind, randomised, phase 2 dose-finding study conducted in Colombia and Panama. Children received one or two intramuscular doses of NoV formulations containing 15/15, 15/50, 50/50 or 50/150 µg of GI.1/GII.4c genotype VLPs and 0.5 mg $Al(OH)_3$. Vaccinations were on Days 1 and 29, with saline placebo as dose two to maintain blinding in one dose groups. Antibody responses to each VLP were measured on days 1, 29 and 57 as functional histo-blood group binding antigen blocking antibodies (HBGA), expressed as seroresponse rates (SRR), the proportions displaying ≥ 4-fold increases over baseline, and geometric mean titres (GMT).

Results: Each formulation induced dosage-dependent HBGA responses after a single dose, with a further increase after a second dose. In 1–< 4 year-olds HBGA SRR against GI.1 and GII.4c after one dose were 55–62% and 67–82%, respectively. SRR increased to 93–100% and 83–100% after a second dose. Responses were lower after the first dose in 6 to < 12 month-olds; SRRs were 10-61% and 17-65% for GI.1 and GII.4c, respectively, increasing to 83–100% and 80–92% after a second dose. GMTs reflected this pattern of responses with higher GMTs for GI.1 and GII.4c achieved with the 50/150 µg formulation than the other dosages after both vaccinations in both age cohorts.

Conclusions: In 6-12 month-old infants and children up to 4 years of age, robust immune responses to the bivalent NoV VLP vaccine candidates were observed; the highest HBGA responses in both age cohorts were observed after two doses of the 50/150 µg formulation. Further clinical evaluation of these formulations is underway in infants < 6 months of age.

Clinical Trial Registration (NCT: 02153112, EudraCT: 2014-000778-20)

INTRODUCTION

Noroviruses have become the leading cause of acute gastroenteritis (AGE) in children in the world, particularly in those countries such as the United States that have implemented routine rotavirus immunization[1]. Although norovirus AGE (NAGE) mainly presents as an acute illness in children without serious sequelae, in the US NAGE results in 1.7–1.9 million outpatient visits and 400,000 emergency department visits, primarily in young children, and 570 to 800 deaths, mostly among young children and the elderly[2]. While seasonal, and mainly occurring during the winter, infection is unpredictable, and there is currently no specific prophylaxis or vaccine available to prevent norovirus infection.

To meet this medical need, Takeda is developing a bivalent norovirus vaccine (NoV) candidate (TAK-214) consisting of two virus-like particle antigens (VLP); one against the GI.1 genotype, and a second consisting of a consensus sequence (GII.4c) containing epitopes from three GII.4 strains to provide broad coverage against the predominant GII circulating genotype[3].

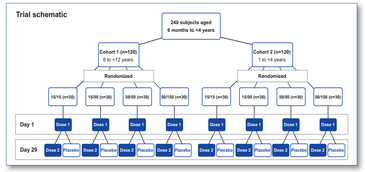
The safety, tolerability and immunogenicity of this vaccine candidate have been established in several clinical trials in adults from 18 years of age and over[4] and we now report on the first interim immunogenicity data of different dosage candidate formulations in children from 6 months to 4 years of age, together with safety and tolerability data from this age group.

PARTICIPANTS AND METHODS

This is a part of a double-blind, randomized, phase 2 dose-finding study performed in Colombia, Finland, and Panama. It will eventually assess TAK-214 in children from 6 weeks to <9 years of age.

- This interim analysis is of part of the study two age cohorts of children of either gender, 6–<12 months (N = 120) and 1–<4 years (N = 120) were enrolled in multiple sites in Colombia and Panama.
  - These two cohorts received vaccine lots prepared in a commercial scale bio-reactor.
  - A third cohort of 1–<4 year-olds (N = 120) that was enrolled in Colombia, Panama and Finland received a vaccine lot prepared in a phase I/II scale bio-reactor has previously been reported[5].
- Each cohort was randomized 1:1:1:1 into four groups to receive intramuscular injections of TAK-214 containing dosages of 15/15, 15/50, 50/50 or 50/150 µg of GI.1/GII.4c VLPs with 0.5 mg $Al(OH)_3$ per dose, respectively (**Trial schematic**).
- Each group was further equally sub-divided to receive either an initial dose (with saline placebo as dose 2) or two doses of TAK-214 28 days apart (**Trial schematic**).
- TAK-214 was given independently at least 28 days before or after routine childhood vaccinations.

Trial schematic



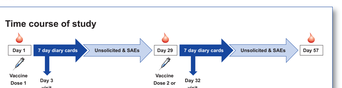
IMMUNOGENICITY ANALYSES

- Blood samples were obtained on Day 1, before the first administration of vaccine, on Day 29 before the second administration of vaccine or placebo, and on Day 57 for immunogenicity analyses.
- Immune responses were measured as functional histo-blood group binding antigen blocking antibodies (HBGA) and Pan-Ig (IgG, IgA, IgM) antibodies against the constituent GI.1 and GII.4c VLPs.
- Responses were expressed as:
  - geometric mean titers (GMT),
  - seroresponse rates (SRR), the proportions displaying ≥ 4-fold increases over baseline,
  - geometric mean-fold increases (GMFR) over baseline.

SAFETY AND REACTOGENICITY ANALYSES

- Safety and reactogenicity of the placebo and vaccine administrations were also assessed using diary cards completed by parents/guardians soliciting local and systemic adverse events (AEs) for 7 days post-vaccination, and unsolicited AEs and serious adverse events (SAEs) until Day 57.

Time course of study



RESULTS

- All groups in both age cohorts were similar with respect to basic demographic data (**Table 1**).

Table 1. Demographics (Per Protocol set)

Age groups	1–<4 year-olds		6–<12 month-olds	
	One dose	Two doses	One dose	Two doses
N =	52	56	52	56
Age ± SD	1.90 ± 0.73 yrs	2.1 ± 0.75 yrs	8.3 ± 1.6 mths	7.9 ± 1.2 mths
Male: n (%)	24 (46.2)	37 (66.1)	28 (53.8)	29 (51.8)
Race, no. (%)				
White	0 (0)	2 (3.6)	2 (38)	0 (0)
American Indian or Alaska Native	11 (21.2)	10 (17.9)	24 (46.2)	29 (51.8)
Black or African American	8 (15.4)	10 (17.9)	7 (13.5)	5 (8.9)
Asian	0 (0)	0 (0)	1 (1.9)	0 (0)
Multiracial	0 (0)	0 (0)	0 (0)	0 (0)
Other	33 (63.5)	34 (60.7)	18 (34.6)	22 (39.3)

BASELINE IMMUNOGENICITY

- Pre-vaccination baseline Pan-Ig antibody titers against both GI.1 and GII.4c were higher in 1–<4 year-old children than in 6–12 month-old infants (**Table 2**), indicating natural age-related exposure to circulating viruses.
- Pre-vaccination baseline titers of HBGA-blocking antibodies were also slightly higher in in the older children than in the infants, more noticeably for GII.4c than GI.1 (**Table 2**).
- This was confirmed by the observation that over 82% of infants were seronegative for HBGA-blocking antibodies and 42–61% did not have Pan-Ig antibodies against the two vaccine antigens. In comparison, 44–79% and 6–7% of 1–<4 year-olds and 6–<12 month-olds did not have Pan-Ig antibodies against GI.1 and GII.4c, respectively.

Table 2. Pre-vaccination HBGA-blocking and Pan-Ig antibody titers

		HBGA-blocking antibodies		Pan-Ig antibodies	
	Age groups	1–<4 year-olds	6–<12 month-olds	1–<4 year-olds	6–<12 month-olds
N = Geometric Mean (95% CI)	GI.1	102 **23.0** (18.9, 28.1)	104 **16.9** (15.2, 18.9)	108 **319** (216, 470)	108 **25.8** (21.1, 31.5)
	GII.4c	105 **53.9** (41.4, 70.1)	97 **17.4** (15.7, 19.4)	108 **1109** (751, 1638)	108 **62.6** (47.7, 82.1)
Baseline seronegative	GI.1	**78.7%**	**91.7%**	**7.4%**	**41.7%**
	GII.4c	44.4%	82.4%	6.5%	61.1%

POST-VACCINATION IMMUNOGENICITY

- Four weeks after vaccination there were marked increases in HBGA-blocking antibody titers to both GI.1 and GII.4c (**Figures 1A** and **B**).
- There was a trend to higher HBGA antibody titers after a second vaccination with higher vaccine doses
  - In both age groups, there were small incremental increases in titers against GI.1 after a single vaccination, but a larger increase after a second vaccination.
  - In 1–<4 year-olds, titers against GII.4c increased after a single vaccination, but did not further increase after a second vaccination.
  - In 6–<12 month-olds, titers against GII.4c showed larger increases after a second vaccination, but remained lower than in the older children.
  - In both age cohorts, there was a pattern of responses with higher GMTs for GI.1 and GII.4c achieved with the highest dose (50/150 formulation) than the other dosages after both vaccinations

Figure 1. Geometric mean titers (GMTs) of (A) GI.1 HGBA-blocking antibodies and (B) GII.4c HGBA-blocking antibodies in the two age cohorts

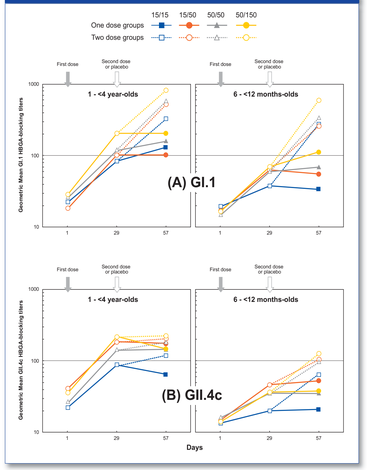
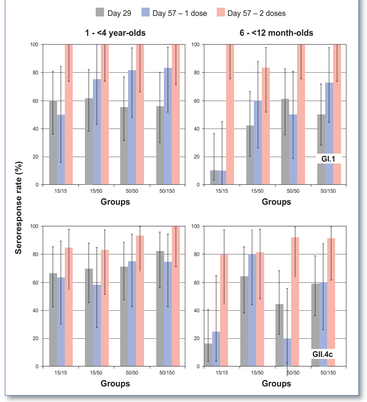


Figure 2. Seroresponse rates (SRR) of GI.1 and GII.4c HGBA-blocking antibodies (with 95% CI) in the four vaccine groups in each of the two age cohorts at Day 29 after one dose (all subjects combined) and Day 57 after one or two doses



- Higher SRR to higher doses of VLP and to a second vaccination were observed in both age cohorts (**Figure 2**)
  - SRR against GI.1 to a single vaccination with any dose in both age groups were low, peaking at approximately 60% at Day 29, with some further increase by Day 57, but were significantly enhanced to 100% in most groups by a second vaccination.
  - The GII.4c response was dose-dependent, and was enhanced by two vaccinations in both age groups.
- These results were reflected in the GMFR against both VLPs in all age groups (**Tables 3A** and **B**).
  - These GMT, SRR and GMFR data support support the use of the highest dose formulation for both norovirus antigens in both age cohorts.

Table 3a. Geometric mean-fold rises (GMFR) in HBGA-blocking antibodies against GI.1 in 1–<4 year-old children and 6–<12 month-old infants

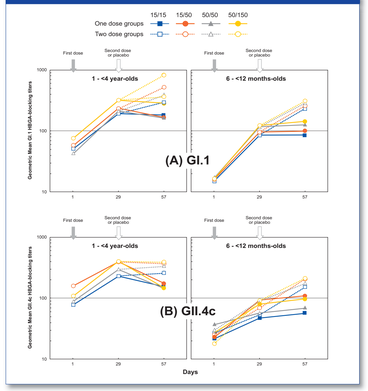
		GMFR (95% CI)			
	Vaccine groups	15/15	15/50	50/50	50/150
1–<4 year-olds	N =	20	21	20	16
	Day 29	**4.72**	**5.47**	**4.63**	**7.38**
		(2.88, 7.72)	(2.54, 11.8)	(2.80, 7.66)	(4.05, 13.5)
	n =	8	12	11	12
	Day 57	**4.24**	**4.96**	**7.53**	**7.86**
	(1 dose)	(1.87, 9.62)	(2.11, 11.7)	(4.52, 12.6)	(4.17, 14.8)
	n =	12	12	14	12
	Day 57	**18.6**	**32.1**	**17.9**	**34.0**
	(2 dose)	(13.1, 26.4)	(19.7, 52.1)	(11.1, 28.9)	(20.3, 56.8)
6–<12 month-olds	N =	20	19	18	22
	Day 29	**1.90**	**3.59**	**3.63**	**4.37**
		(1.32, 2.74)	(2.21, 5.85)	(2.46, 5.35)	(2.71, 7.05)
	n =	10	10	10	10
	Day 57	**1.65**	**3.74**	**4.04**	**7.41**
	(1 dose)	(0.95, 2.85)	(1.80, 7.74)	(1.87, 8.72)	(4.25, 12.9)
	n =	13	12	13	12
	Day 57	**16.9**	**13.3**	**22.1**	**32.4**
	(2 dose)	(11.6, 24.6)	(5.75, 31.0)	(14.7, 33.2)	(22.0, 47.6)

Table 3b. Geometric mean-fold rises (GMFR) in HBGA-blocking antibodies against GII.4c in 1–<4 year-old children and 6–<12 month-old infants

		GMFR (95% CI)			
	Vaccine groups	15/15	15/50	50/50	50/150
1–<4 year-olds	N =	21	20	21	17
	Day 29	**7.64**	**11.8**	**11.8**	**15.6**
		(2.88, 7.72)	(2.54, 11.8)	(2.80, 7.66)	(4.05, 13.5)
	n =	11	12	12	12
	Day 57	**6.53**	**6.13**	**13.0**	**9.07**
	(1 dose)	(1.87, 9.62)	(2.11, 11.7)	(4.52, 12.6)	(4.17, 14.8)
	n =	13	12	15	11
	Day 57	**10.1**	**17.3**	**16.2**	**20.6**
	(2 dose)	(13.1, 26.4)	(19.7, 52.1)	(11.1, 28.9)	(20.3, 56.8)
6–<12 month-olds	N =	18	17	20	22
	Day 29	**1.54**	**6.46**	**3.94**	**4.36**
		(1.32, 2.74)	(2.21, 5.85)	(2.46, 5.35)	(2.71, 7.05)
	n =	8	10	10	10
	Day 57	**2.00**	**5.43**	**3.33**	**5.64**
	(1 dose)	(0.95, 2.85)	(1.80, 7.74)	(1.87, 8.72)	(4.25, 12.9)
	n =	10	11	13	12
	Day 57	**9.52**	**15.1**	**17.8**	**29.4**
	(2 dose)	(11.6, 24.6)	(5.75, 31.0)	(14.7, 33.2)	(22.0, 47.6)

- When responses were measured as Pan-Ig antibodies to the two vaccine antigens the same patterns were observed (**Figure 3**).
  - In 1–<4 year-olds there was a dose-independent GI.1 response to one dose and a small further increase after a second vaccination.
  - In 6–<12 month-olds the GI.1 response to a second vaccination was more apparent, achieving titers similar to those from the older children but from a lower prevaccination baseline.
  - Pan-Ig against GII.4c increased after one vaccination in 1–<4 year-olds, with no further increase after a second vaccination.
  - Pan-Ig against GII.4c in 6–<12 month-olds increased after both vaccinations to achieve mean titers similar to those observed at baseline from the older children.
- Similar observations were made in the previously reported 1–<4 year-old cohort which received phase I/II vaccine manufactured on a smaller scale for phase I/II studies.

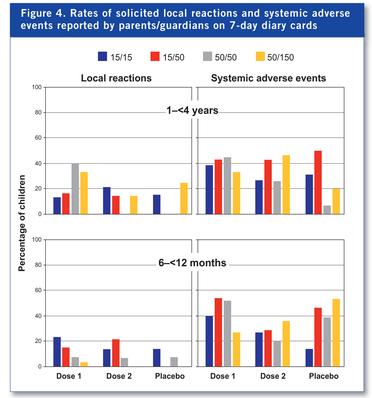
Figure 3. Geometric mean titers (GMT) of Pan-Ig GI.1 and GII.4c antibodies in the different vaccine groups in the two age cohorts



SAFETY AND TOLERABILITY

- All dosages of NoV were generally well tolerated and no safety signal was detected.
- There were no causally related SAEs reported during this phase of the study in either age cohort.
- No participant was withdrawn due to any vaccine-related adverse event.
- There were no dosage-associated increases in solicited local reactions or systemic AEs (**Figure 4**).
  - Local reactions were more frequent in 1–<4 year-olds than 6–<12 month-olds.
  - Systemic AEs were reported at similar rates across dosages in both age cohorts.
- Local reactions and systemic AEs were transient, mainly mild or moderate in severity and did not increase with a second dose.
- Temperature ≥ 38°C was infrequent in all groups in both age cohorts.

Figure 4. Rates of solicited local reactions and systemic adverse events reported by parents/guardians on 7-day diary cards



CONCLUSIONS

- All four dosages of the TAK-214 norovirus vaccine candidate were immunogenic in children from 6 months to < 4 years of age.
- A two-dose regimen of TAK-214 was more immunogenic than one-dose across this age range.
- The magnitude of responses was lower in the younger age cohort - which has probably had less natural exposure to norovirus at baseline - than the older age cohort, where a second dose did not increase antibody GMTs but did improve seroresponse rates.
- There was some evidence of a dose-dependent effect on the magnitude of the responses in both age groups.
- Across the age range from 6 months to < 4 years the different dosages of TAK-214 candidate formulations were well tolerated and had a clinically acceptable safety profile, with no vaccine-related SAEs or AEs leading to withdrawal.
- These immunogenicity and safety data support the use of the highest dose formulation (50/150 µg of GI.1/GII.4c VLPs) in a two-dose schedule in the age range studied, 6 months to 4 years.
- Further studies are ongoing to assess TAK-214 in younger children.

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ACKNOWLEDGEMENTS

We are grateful to all the participating children and their parents, and to all of the staff at each of the study centers, especially **Dr. Xavier Saez-Llorens** & the site staff, CEVAXIN Plaza Carolina, Panama and **Dr. Pio Lopez, Dr. Eduardo Lopez** & the site staff, Centro de Estudios en Infectología Pediátrica S.A.S., Colombia

(1) This work is supported by the US Army Medical Research and Materiel Command under Contract No. W81XWH-15-C-0063

(2) The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

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