Safety and Tolerability of Takeda's Bivalent Virus-Like Particle (VLP) Norovirus Vaccine (NoV) in Children

Taisei Masuda, Paul M Mendelman, Michael Hellwig, Jim Sherwood, Frank Baehner, Astrid Borkowski

Takeda Pharmaceuticals AG, Zurich. Switzerland

OBJECTIVES

Since the introduction of routine rotavirus immunisation noroviruses (NoV) have become the leading cause of acute gastroenteritis (AGE) in children in the world¹. Although mainly an acute illness in most children without serious sequelae, NoV AGE is estimated to cause 102 deaths (95% CI 69–139) in children under 5 years of age in Europe each year². There is currently no vaccine available against norovirus infection.

Takeda is developing a bivalent norovirus vaccine (NoV) candidate consisting of two virus-like particle antigens (VLP); one against the GI.1 genotype, and a second consisting of a consensus sequence (GI.4c) containing epitopes from three GI.4 strains to provide broad coverage against the predominant circulating genotype³.

We have established the safety, tolerability and immunogenicity of this vaccine candidate in adults⁴ and we now report on the first interim data of the safety and tolerability of different dosage candidate formulations in children from 1 through 8 years of age. Immunogenicity data from this study are the subject of an oral presentation (Abstract: ESP18-0787).

1. Payne DC, et al. Norovirus and medically attended gastroenteritis in U.S. children. *N Engl J Med* 2013; 368:1121–30.
2. Kowalzik F, et al. Burden of Norovirus Disease in Children in the European Union. *Pediatr Infect Dis J* 2015;34:229–34.
3. Parra GI, et al. Immunogenicity and specificity of norovirus Consensus GI.4 virus-like particles in monovalent and bivalent vaccine formulations. *Vaccine* 2012;30:3580–6.
4. Baehner F, et al. Vaccines against norovirus: state of the art trials in children and adults. *Clin Microbiol Infect* 2016;22 Suppl 5:S136–9.

PARTICIPANTS AND METHODS

This is an ongoing double-blind, randomized, phase 2 dose-finding study performed in Colombia, Finland, and Panama, registered with ClinicalTrials.gov NCT:02153112. It will eventually assess NoV in children from 6 weeks to <9 years of age.

- In this first part of the study two age cohorts of children of either sex, 4–<9 years and 1–<4 years, 120 per cohort, were enrolled.
- Each cohort was randomized 1:1:1:1 into four groups to receive intramuscular injections of NoV containing dosages of 15/15, 15/50, 50/50 or 50/150 µg of GI.1/GI.4c VLPs, respectively.
- Each group was further equally sub-divided to receive either an initial dose (with saline placebo as dose 2) or two doses of NoV 28 days apart (see **Figure 1**, Trial schematic).
- Parents completed diary cards for 7 days after each vaccination (**Figure 2**) on which were solicited:
 - local reactions: injection site pain, erythema, induration, swelling
 - systemic adverse events in 4–<9 year-olds: headache, fatigue, myalgia, arthralgia, vomiting, diarrhea
 - systemic adverse events in 1–<4 year-olds: irritability/fussiness, drowsiness, loss of appetite, vomiting, diarrhea
 - Body temperature was also recorded each day.

Figure 1. Trial schematic

Figure 2. Time course of study

- Parents recorded on the diary cards any unsolicited adverse events or serious adverse events (SAE) until the next study visit (28 days after each vaccination); these AEs were subsequently coded using MedDRA definitions.
- All adverse events were graded for severity and for systemic and unsolicited AEs the relationship to the vaccination was assessed by the investigator.
- All local reactions and AEs are reported as incidence rates, i.e. percentages of subjects with at least one solicited AEs in the respective treatment group.

RESULTS

- Groups were similar with respect to basic demographic data, with no differences in terms of age, gender or ethnicity.
- Mean ages were 5.7–6.4 years in the 4–<9 year-old groups, and 1.8–2.3 years in the 1–<4 year-old groups.
- In 4–<9 year-olds, 55% were enrolled in Finland, 8% in Colombia and 37% in Panama.
- In 1–<4 year-olds, 52% were enrolled in Finland, 32% in Colombia and 16% in Panama.
- 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 3**).

Figure 3.

- Local reactions were more frequent in 4–<9 year-olds (61.7% after first dose across dosages) than 1–<4 year-olds (26.7% after first dose across dosages).
- Systemic AEs were reported at similar rates across dosages in 4–<9 year-olds (47.5% after first dose across dosages) and 1–<4 year-olds (40.0% after first dose).
- Rates of both local reactions and systemic AEs were lower after a second dose, and higher than placebo in most instances.
- The majority of solicited AEs were mild to moderate in severity, and resolved within the reporting period.
- The most frequent local reaction was injection site pain in both age cohorts (**Figure 4**).
- The majority of local reactions were described as mild or moderate, with few described as severe.
- Other local reactions were minimal (< 4.2%).

Figure 4.

- Most frequent systemic AEs were headache, fatigue and myalgia in 4–<9 year-olds (**Table 1**)
- Rates decreased with the second dose and were lowest with placebo
- In 1–<4 year-olds irritability, drowsiness and loss of appetite were the most frequent AEs (**Table 1**)
- Rates of irritability and loss of appetite were similar after the second dose

Table 1. Incidence (%) of solicited systemic AEs in the 7 days after NoV doses 1 & 2, and Placebo

Group	First dose				Second dose				Placebo			
	15/15	15/50	50/50	50/150	15/15	15/50	50/50	50/150	15/15	15/50	50/50	50/150
4–<9 year-olds												
N =	29	30	30	31	14	14	16	15	15	16	14	16
Headache	21.4	13.3	23.3	20.0	7.7	7.1	25.0	13.3	6.7	12.5	15.4	0
Fatigue	25.0	30.0	13.3	13.3	7.7	28.6	18.8	6.7	13.3	12.5	0	14.3
Myalgia	21.4	16.7	30.0	13.3	7.7	0	25.0	6.7	6.7	0	15.4	7.1
Arthralgia	3.6	3.3	3.3	3.3	0	0	0	0	0	0	7.7	0
Vomiting	10.7	0	3.3	10.0	0	0	0	0	6.7	0	0	0
Diarrhoea	7.7	10.3	7.4	6.9	9.1	0	7.1	6.7	0	0	0	0
1–<4 year-olds												
N =	31	30	29	30	15	14	15	15	16	16	14	15
Irritability	19.4	20.0	24.1	23.3	13.3	21.4	14.3	33.3	26.7	26.7	0	0
Drowsiness	16.1	10.0	17.2	13.3	6.7	7.1	14.3	6.7	6.7	13.3	0	6.7
Loss of appetite	23.3	31.0	26.7	6.7	28.6	14.3	33.3	20.0	13.3	7.1	6.7	0
Vomiting	6.5	3.3	10.3	0	0	0	0	6.7	0	0	0	6.7
Diarrhoea	12.9	13.3	10.3	13.3	0	0	7.1	26.7	13.3	20.0	0	0

- Temperature $\geq 38^{\circ}\text{C}$ was infrequent in all groups in both age cohorts (**Figure 5**).

Figure 5.

- Unrelated AEs were reported at similar rates across groups (**Table 2**).
- Most were considered to be unrelated to the vaccinations

Table 2. Incidence (%) and relatedness of unsolicited AEs in the 28 days after NoV doses 1 & 2, and Placebo

Group	First dose				Second dose				Placebo			
	15/15	15/50	50/50	50/150	15/15	15/50	50/50	50/150	15/15	15/50	50/50	50/150
4–<9 year-olds												
N =	29	30	30	31	14	14	16	15	15	16	14	16
Adverse events	37.9	33.3	50.0	35.5	42.9	14.3	31.3	33.3	33.3	31.3	35.7	31.3
Related	3.4	6.7	3.3	9.7	7.1	7.1	0	0	0	0	0	6.3
Unrelated	34.5	26.7	46.7	25.8	35.7	7.1	31.3	33.3	33.3	31.3	35.7	25.0
1–<4 year-olds												
N =	31	30	29	30	15	14	15	15	16	16	14	15
Adverse events	61.3	53.3	48.3	46.7	46.7	42.9	33.3	53.3	50.0	43.8	21.4	26.7
Related	3.2	3.3	10.3	3.3	0	0	6.7	6.7	0	0	7.1	0
Unrelated	58.1	50.0	37.9	43.3	46.7	42.9	26.7	46.7	50.0	43.8	14.3	26.7

CONCLUSIONS

- Across the age range from 1 year to < 9 years the different dosages of NoV candidate formulations were well tolerated and had a clinically acceptable safety profile.
- No vaccine-related SAEs or AEs leading to withdrawal were reported.
- Local reactions and systemic AEs were transient and mainly mild or moderate in severity, with no increase after a second dose in either age cohort.
- Incidence and severity of AEs were not VLP dosage-related.

ACKNOWLEDGEMENTS

We are grateful to all the participants and their parents, and to all of the staff at each of the study centers. In particular:

Prof. Timo Vesikari, University of Tampere Medical School, Finland, and his collaborators: Dr. Anitta Ahonen, Dr. Tiina Karpaa, Dr. Aino Forstén, Dr. Marita Paassilta, Dr. Satu S. Kokko, Dr. Tiina Korhonen, Dr. Ilkka Seppä and their staff at Järvenpää, Etelä-Helsinki, Pori, Seinäjoki, Itä-Helsinki, Espoo, Oulu, Tampere and Turku sites.

Dr. Xavier Saez-Llorens & the site staff, CEVAXIN Plaza Carolina, Panama

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.

(3) The investigator(s) adhered to the policies regarding the protection of human subjects as prescribed by Code of Federal Regulations (CFR) Title 45, Volume 1, Part 46, Title 32, Chapter 1, Part 219, and Title 21, Chapter 1, Part 50 (Protection of Human Subjects).