Title: Phase 2b bivalent GI.1/GII.4c norovirus vaccination in infants and serologic evidence that pre-existing immunity is required for broad GII.4 neutralization

Supplemental Index

Contents

NOR-212: Patient disposition and demographics

Table S1. NOR-212 (NEST-IN1) participant disposition (randomized participants).

Category		Number of Participants, n (%)		
		HIL-214 (N=1542)	Placebo (N=1542)	Total (N=3084)
Two vaccinations		1425 (92.4)	1399 (90.7)	2824 (91.6)
One vaccination		115 (7.5)	139 (9.0)	254 (8.2)
No vaccination		2 (0.1)	4 (0.3)	6 (0.2)
Discontinuation from vaccine regimen		117 (7.6)	143 (9.3)	260 (8.4)
Primary reason:	Adverse event	1 (<0.1)	1 (<0.1)	2 (<0.1)
	Lost to follow-up	11 (0.7)	14 (0.9)	25 (0.8)
	Withdrawal by LAR	74 (4.8)	90 (5.8)	164 (5.3)
	Protocol deviation	4 (0.3)	11 (0.7)	15 (0.5)
	Other	27 (1.8)	27 (1.8)	54 (1.8)
Visit 2 completed: Age: ~6 mos		1462 (94.8)	1434 (93.0)	2896 (93.9)
Discontinued from Trial (by Visit 2/Day 43)		80 (5.2)	107 (6.9)	187 (6.1)
Primary reason:	Adverse event	0	1 (<0.1)	1 (<0.1)
	Lost to follow-up	9 (0.6)	14 (0.9)	23 (0.7)
	Withdrawal by LAR	70 (4.5)	84 (5.4)	154 (5.0)
	Other	0	4 (0.3)	4 (0.1)
Visit 3 completed; Age: ~7 mos		1441 (93.5)	1417 (91.9)	2858 (92.7)
Discontinued from Trial (by Visit 3/Day 71)		101 (6.5)	125 (8.1)	226 (7.3)
Primary reason:	Adverse event	0	1 (<0.1)	1 (<0.1)
	Lost to follow-up	14 (0.9)	19 (1.2)	33 (1.1)
	Withdrawal by LAR	86 (5.6)	99 (6.4)	185 (6.0)
	Other	1 (<0.1)	4 (0.3)	5 (0.2)
Visit 4 completed; Age: 1 yr		1414 (91.7)	1392 (90.3)	2806 (91.0)
Discontinued from Trial (by Visit 4/Day 210)		128 (8.3)	150 (9.7)	278 (9.0)
Primary reason:	Adverse event	0	1 (<0.1)	1 (<0.1)
	Lost to follow-up	22 (1.4)	28 (1.8)	50 (1.6)
	Withdrawal by LAR	98 (6.4)	113 (7.3)	211 (6.8)
	Death	2 (0.1)	0	2 (<0.1)
	Other	5 (0.3)	8 (0.5)	13 (0.4)
Primary analysis completed; Age: ~13 mos		1410 (91.4)	1381 (89.6)	2791 (90.5)
Discontinued from Trial (by 6 months AGE surveillance)		132 (8.6)	161 (10.4)	293 (9.5)
Primary reason:	Adverse event	0	1 (<0.1)	1 (<0.1)
	Lost to follow-up	22 (1.4)	29 (1.9)	51 (1.7)
	Withdrawal by LAR	103 (6.7)	122 (7.9)	225 (7.3)
	Death	2 (0.1)	1 (<0.1)	3 (0.1)
	Other	5 (0.3)	8 (0.5)	13 (0.4)
Visit 5 completed: Age: 18 mos		1399 (90.7)	1364 (88.5)	2763 (89.6)
Discontinued from Trial (by Visit 5/Day 390)		143 (9.3)	176 (11.4)	319 (10.3)
Primary reason:	Adverse event	0	1 (<0.1)	1 (<0.1)
	Lost to follow-up	25 (1.6)	34 (2.2)	59 (1.9)
	Withdrawal by LAR	105 (6.8)	130 (8.4)	235 (7.6)
	Death	2 (0.1)	1 (<0.1)	3 (<0.1)
	Other	11 (0.7)	10 (0.6)	21 (0.7)
Final analysis completed; Age: 2 yrs		1178 (76.4)	1142 (74.1)	2320 (75.3)
Discontinued from Trial (by Visit 6/Day 570; ~16 months AGE surveillance)		363 (23.5)	398 (25.8)	761 (24.7)
Primary reason:	Adverse event	0	1 (<0.1)	1 (<0.1)
	Lost to follow-up	34 (2.2)	42 (2.7)	76 (2.5)
	Withdrawal by LAR	111 (7.2)	135 (8.8)	246 (8.0)
	Death	2 (0.1)	1 (<0.1)	3 (<0.1)
	Other	216 (14.0)	219 (14.2)	435 (14.1)

Abbreviation: LAR, legally authorized representative.

Table S2. Characteristics of the enrolled and randomized population in NOR-212 study (FAS)

Category	Number of Participants, n (%)		
	HIL-214 (N=1540)	Placebo (N=1538)	Total (N=3078)
Age, months			
Mean (SD)	5.0 ± 0.3	4.9 ± 0.3	5.0 ± 0.3
Gender, n (%)			
Female	777 (50.5)	800 (52.0)	1577 (51.2)
Male	763 (49.5)	738 (48.0)	1501 (48.8)
Ethnicity, n (%)			
Hispanic or Latino	1521 (98.8)	1520 (98.8)	3041 (98.8)
Unknown	14 (0.9)	14 (0.9)	28 (0.9)
Not Hispanic or Latino	5 (0.3)	4 (0.3)	9 (0.3)
Race, n (%)			
Other	1429 (92.8)	1429 (92.9)	2858 (92.9)
Not Reported	72 (4.7)	61 (4.0)	133 (4.3)
Unknown	15 (1.0)	16 (1.0)	31 (1.0)
Black or African American	10 (0.6)	14 (0.9)	24 (0.8)
Multiracial	10 (0.6)	12 (0.8)	22 (0.7)
White	3 (0.2)	5 (0.3)	8 (0.3)
American Indian or Alaska Native	0	1 (<0.1)	1 (<0.1)
Asian	1 (<0.1)	0	1 (<0.1)
Country, n (%)			
Panama	818 (53.1)	817 (53.1)	1635 (53.1)
Dominican Republic	310 (20.1)	308 (20.0)	618 (20.1)
Honduras	260 (16.9)	260 (16.9)	520 (16.9)
Peru	105 (6.8)	105 (6.8)	210 (6.8)
Colombia	43 (2.8)	44 (2.9)	87 (2.8)
Puerto Rico	3 (0.2)	3 (0.2)	6 (0.2)
United States of America	1 (<0.1)	1 (<0.1)	2 (<0.1)

Abbreviations: SD, standard deviation; FAS, Full Analysis Set.

NOR-212: AGE Cases

Table S3. Overview of all AGE events and evaluable RT-PCR confirmed norovirus AGE events during the 6-month and ~16-month AGE surveillance periods in the NOR-212 study (mFAS)

Category		Number of Participants/Events, n (%)			
		HIL-214 (N=1425)		Placebo (N=1399)	
		6 mos AGE surveillance	~16 mos AGE surveillance	6 mos AGE surveillance	~16 mos AGE surveillance
Number of participants with AGE events, N_P[a]		**491 (34.5)**	**856 (60.1)**	**482 (34.5)**	**836 (59.8)**
Number of AGE events, N_A		**851**	**2536**	**829**	**2445**
Number of participants with norovirus AGE events, N_N[c]		**170 (11.9)**	**319 (22.4)**	**170 (12.2)**	**318 (22.7)**
Number of participants with norovirus AGE by number of events[d]	1	145 (85.3)	236 (74.0)	144 (84.7)	228 (71.7)
	2	23 (13.5)	67 (21.0)	22 (12.9)	62 (19.5)
	3	2 (1.2)	16 (5.0)	3 (1.8)	25 (7.9)
	4	0	0	0	1 (0.3)
	≥5	0	0	0	2 (0.6)
Number of norovirus AGE events, N_{NA}		**197**	**418**	**202**	**442**
Number of norovirus AGE events by severity grading[e]	No score	21 (10.7)	0	24 (11.9)	0
	Mild	92 (46.7)	238 (56.9)	98 (48.5)	240 (54.3)
	Moderate	30 (15.2)	75 (17.9)	30 (14.9)	83 (18.8)
	Severe	54 (27.4)	105 (25.1)	50 (24.8)	119 (26.9)
Number of norovirus events by genogroup[e]	GI	44 (22.3)	83 (19.9)	31 (15.3)	71 (16.1)
	GII	158 (80.2)	342 (81.8)	173 (85.6)	377 (85.3)
	GI & GII	5	7	2	6
Number of norovirus AGE events with norovirus genotype, N_T		**161**	**346**	**161**	**356**
Number of norovirus AGE events by genotype[f,g]	GI.1	0	0	0	0
	GII.4	69 (42.9)	123 (35.5)	69 (42.9)	121 (34.0)
	GI.2	0	0	1 (0.6)	2 (0.6)
	GI.3	8 (5.0)	19 (5.5)	4 (2.5)	9 (2.5)
	GI.4	1 (0.6)	1 (0.3)	0	0
	GI.5	21 (13.0)	35 (10.1)	18 (11.2)	41 (11.5)
	GI.6	1 (0.6)	1 (0.3)	0	2 (0.6)
	GI.7	0	2 (0.6)	0	1 (0.3)
	GII.1	1 (0.6)	7 (2.0)	1 (0.6)	7 (2.0)
	GII.2	1 (0.6)	3 (0.9)	0	0
	GII.3	1 (0.6)	6 (1.7)	2 (1.2)	5 (1.4)
	GII.6	11 (6.8)	30 (8.7)	12 (7.5)	29 (8.1)
	GII.7	3 (1.9)	18 (5.2)	2 (1.2)	15 (4.2)
	GII.8	2 (1.2)	7 (2.0)	4 (2.5)	7 (2.0)
	GII.9	2 (1.2)	3 (0.9)	0	1 (0.3)
	GII.10	0	1 (0.3)	0	3 (0.8)
	GII.12	0	2 (0.6)	0	5 (1.4)
	GII.14	0	10 (2.9)	2 (1.2)	19 (5.3)
	GII.17	37 (23.0)	74 (21.4)	40 (24.8)	80 (22.5)
	GII.21	1 (0.6)	1 (0.3)	3 (1.9)	3 (0.8)
	GII.27	2 (1.2)	3 (0.9)	2 (1.2)	5 (1.4)
	GIX.1	0	0	1 (0.6)	1 (0.3)
Number of norovirus AGE events with co-infection, N_C		**107**	**253**	**90**	**266**
Number of norovirus AGE event by other GE pathogen[h]	Any	89 (83.2)	202 (79.8)	75 (83.3)	208 (78.2)
	Multiple	16 (15.0)	45 (17.8)	13 (14.4)	47 (17.7)
	Camplyobacter	26 (24.3)	53 (20.9)	30 (33.3)	59 (22.2)

	E.Coli (ETEC)	28 (26.2)	47 (18.6)	23 (25.6)	49 (18.4)
	Salmonella	26 (24.3)	90 (35.6)	20 (22.2)	112 (42.1)
	Shigella	15 (14.0)	37 (14.6)	9 (10.0)	28 (10.5)
	Cryptosporidium	4 (3.7)	11 (4.3)	5 (5.6)	10 (3.8)
	Rotavirus	7 (6.5)	11 (4.3)	0	4 (1.5)
	Adenovirus DNA	1 (0.9)	4 (1.6)	3 (3.3)	4 (1.5)

a. Percentage (%) = N_P/N.
b. Percentage (%) = N_N/N.
c. Percentage (%) = n/N_N.
d. AGE severity grading based on non-imputed modified Vesikari score[1].
e. Percentage (%) = n/N_{NA}.
f. Percentage (%) = n/N_T.
g. Norovirus genotyping performed by CDC was used for analyses.
h. Percentage (%) = n/N_C

Abbreviations: AGE, acute gastroenteritis; GE, gastroenteritis; mFAS, modified Full Analysis Set.

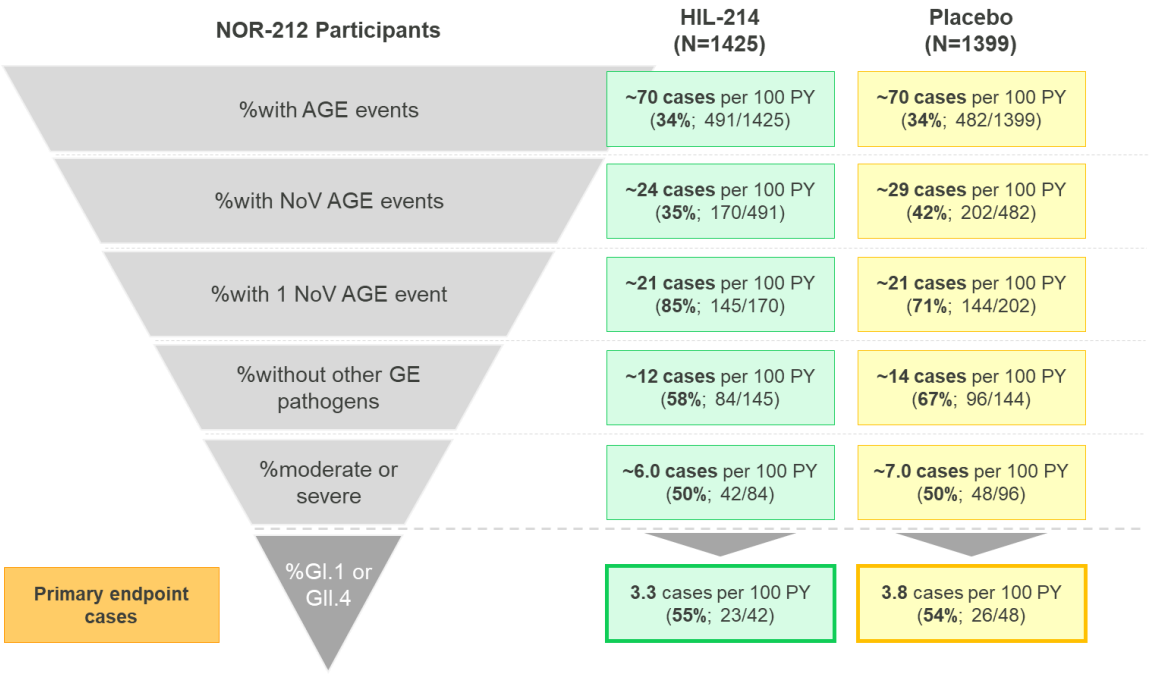


Figure S1. Evaluation of placebo AGE case accrual against expected epidemiologic incidence rates during the 6-month AGE surveillance period in the NOR-212 study.

NOR-212: Efficacy

Table S4. Concordance of vaccine efficacy estimates between Cox proportional hazard and Poisson regression models during the 6-month AGE surveillance period in the NOR-212 study (mFAS).

Norovirus genotypes or genogroups	AGE symptom severity	Number of Participants with Events, n (%)[a]		Vaccine efficacy, % (95% CI)[b]	Vaccine efficacy, % (95% CI)[c]
		HIL-214 (N=1425)	Placebo (N=1399)		
		6 mos AGE surveillance	6 mos AGE surveillance	6 mos AGE surveillance	6 mos AGE surveillance
First GI.1 or GII.4	Mod/Sev	23 (1.6)	26 (1.9)	14 (-53 to 50)	13 (-52 to 51)
First GI.1 or GII.4	Mild	16 (1.1)	18 (1.3)	12 (-72 to 55)	12 (-72 to 55)
First GI.1 or GII.4	Mild/Mod/Sev	39 (2.7)	43 (3.1)	11 (-38 to 42)	11 (-37 to 42)
First GI or GII	Mod/Sev	43 (3.0)	51 (3.6)	17 (-25 to 45)	17 (-24 to 45)
First GI or GII	Mild	46 (3.2)	55 (3.9)	18 (-22 to 44)	18 (-22 to 44)
First GI or GII	Mild/Mod/Sev	88 (6.2)	103 (7.4)	16 (-11 to 37)	16 (-11 to 37)

a. Percentage (%) = n/N.

b. Primary, secondary, and exploratory efficacy endpoint analyses (grey shaded column): Vaccine efficacy is defined 100%[1– (λV/λC)], where λV and λC denote the hazard rates for the HIL-214 and Placebo arms respectively, obtained via a stratified Cox proportional hazards model, using Efron's method for handling ties. The model includes a term for vaccine arm and is stratified by country, whereby United States, Dominican Republic and Puerto Rico were considered one country. The 95% confidence interval is calculated by subtracting the confidence limits of hazard ratio from 1.

c. Sensitivity analyses of primary, secondary, and exploratory efficacy endpoints (unshaded column): Vaccine efficacy is defined 100%[1– (IRR), where IRR is the Incidence Rate Ratio, calculated as the exponent of the coefficient of the trial arm group in a Poisson regression model with log-transformed time to event variable and adjusted by country, whereby United States, Dominican Republic and Puerto Rico were considered one country. The 95% confidence interval of the IRR is also based on the Poisson distribution.

Abbreviations: AGE, acute gastroenteritis; GE, gastroenteritis; CI, confidence interval; mFAS, modified Full Analysis Set

Table S5. Distribution of participants included in GII.4 sNAb breadth analyses among participants with a first GII.4-associated AGE event through the 6-month AGE surveillance period, stratified by variant, severity, and country in the NOR-212 study.

Category, n (%)	Number of participants, n/N (%)[a, b]					
	6 mos AGE surveillance; Included (AGE > Visit 3 < Visit 4)/Total Observed					
	Mod/Sev GII.4 AGE		Mild GII.4 AGE		Mild/Mod/Sev GII.4 AGE	
	HIL-214 (N=16/23)	Placebo (N=12/26)	HIL-214 (N=10/16)	Placebo (N=12/18)	HIL-214 (N=26/39)	Placebo (N=24/44)
GII.4 variant						
GII.4_SF	**5/7 (71)**	**5/12 (42)**	**8/12 (67)**	**6/10 (60)**	**13/19 (68)**	**11/22 (50)**
Panama	5/7 (71)	3/6 (50)	6/9 (67)	5/8 (63)	11/16 (69)	8/14 (57)
Dominican Republic	0	0	0	0	0	0
Honduras	0	1/5 (20)	0/1 (0)	0/1 (0)	0/1 (0)	1/6 (17)
Peru	0	0	2/2 (100)	0	2/2 (100)	0
Colombia	0	1/1 (100)	0	1/1 (0)	0	2/2 (100
Puerto Rico	0	0	0	0	0	0
United States	0	0	0	0	0	0
GII.4_SY	**7/8 (88)**	**6/10 (60)**	**1/1 (100)**	**4/4 (100)**	**8/9 (89)**	**10/14 (71)**
Panama	6/7 (86)	3/6 (5)	1/1 (100)	3/3 (100)	7/8 (88)	6/9 (67)
Dominican Republic	0	1/2 (50)	0	0	0	1/2 (50)
Honduras	1/1 (100)	0	0	1/1 (100)	1/1 (100)	1/1 (100)
Peru	0	0	0	0	0	0
Colombia	0	2/2 (100)	0	0	0	2/2 (100)
Puerto Rico	0	0	0	0	0	0
United States	0	0	0	0	0	0
GII.4_WI	**4/7 (57)**	**0/2 (0)**	**1/1 (100)**	**2/3 (67)**	**5/8 (63)**	**2/5 (40)**
Panama	0	0	0	0	0	0
Dominican Republic	0	0	0	0	0	0
Honduras	4/7 (57)	0/2 (0)	1/1 (100)	2/3 (67)	5/8 (63)	2/5 (40)
Peru	0	0	0	0	0	0
Colombia	0	0	0	0	0	0
Puerto Rico	0	0	0	0	0	0
United States	0	0	0	0	0	0
GII.4_AL	**0**	**0**	**0/1 (0)**	**0/1 (0)**	**0/1 (0)**	**0/1 (0)**
Panama	0	0	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)
Dominican Republic	0	0	0	0	0	0
Honduras	0	0	0	0	0	0
Peru	0	0	0	0	0	0
Colombia	0	0	0	0	0	0
Puerto Rico	0	0	0	0	0	0
United States	0	0	0	0	0	0
GII.4_N/A	**0/1 (0)**	**1/2 (50)**	**0/1 (0)**	**0**	**0/2 (0)**	**1/2 (50)**
Panama	0/1 (0)	1/2 (50)	0/1 (0)	0	0/2	1/2 (50)
Dominican Republic	0	0	0	0	0	0
Honduras	0	0	0	0	0	0
Peru	0	0	0	0	0	0
Colombia	0	0	0	0	0	0
Puerto Rico	0	0	0	0	0	0
United States	0	0	0	0	0	0

a. Among the 39 HIL-214 recipients that experienced a GII.4-associated AGE event of any severity through 6-months AGE surveillance, 28 of 39 (71.8%) occurred after Visit 3 and before Visit 4 (16 mod/sev, 12 mild) and 26 of 28 (92.9%) had serum available for GII.4 sNAbT breadth evaluation.

b. Among the 44 placebo recipients that experienced a GII.4-associated AGE event of any severity through 6-months AGE surveillance, 29 of 44 (65.9%) occurred after Visit 3 and before Visit 4 (16 mod/sev, 13 mild) and 24 of 29 (82.7%) had serum available for analysis.

Abbreviations: AGE, acute gastroenteritis; AL, Allegany; N/A, not typeable; SF, San Francisco; SY, Sydney; WI, Wichita

Table S6. Vaccine efficacy against second AGE events by norovirus genotype/genogroup and symptom severity, excluding other GE pathogens during the 6-month and ~16-month AGE surveillance periods in the NOR-212 study (mFAS).

Norovirus genotypes or genogroups	AGE symptom severity	Number of Participants with Events, n (%)				Vaccine efficacy,[h,i], % (95% CI)	
		HIL-214 (N=1425)		Placebo (N=1399)			
		6 mos AGE surveillance	~16 mos AGE surveillance	6 mos AGE surveillance	~16 mos AGE surveillance	6 mos AGE surveillance	~16 mos AGE surveillance
First GI.1 or GII.4[a]	**Mod/Sev**	**23 (1.6)**	**44 (3.1)**	**26 (1.9)**	**41 (2.9)**	**13 (-53 to 50)**	**-5 (-61 to 31)**
First GII.4, N_1[a]	**Mod/Sev**	**23 (1.6)**	**44 (3.1)**	**26 (1.9)**	**41 (2.9)**	**13 (-53 to 50)**	**-5 (-61 to 31)**
Second GII.4[b]	Mod/Sev	0	0	1 (3.8)	1 (2.4)	N/A	N/A
Second GII.4[b]	Mild	1 (4.3)	1 (2.3)	1 (3.8)	1 (2.4)	-27 (-1934 to 92)	-4 (1564 to 93)
Second GII.4[b]	Mild/Mod/Sev	1 (4.3)	1 (2.3)	2 (7.7)	2 (4.8)	36 (-602 to 94)	48 (-474 to 95)
Second GII (non-GII.4)[b]	Mod/Sev	0	0	1 (3.8)	3 (6.8)	NE	NE
Second GII (non-GII.4)[b]	Mild	0	0	0	0	NE	NE
Second GII (non-GII.4)[b]	Mild/Mod/Sev	0	0	1 (3.8)	3 (6.8)	NE	NE
First GI.1 or GII.4[a]	**Mild**	**16 (1.1)**	**25 (1.8)**	**18 (1.3)**	**22 (1.6)**	**12 (-72 to 55)**	**-11 (-97 to 37)**
First GII.4, N_2[a]	**Mild**	**16 (1.1)**	**25 (1.8)**	**18 (1.3)**	**22 (1.6)**	**12 (-72 to 55)**	**-11 (-97 to 37)**
Second GII.4[c]	Mod/Sev	0	0	0	0	NE	NE
Second GII.4[c]	Mild	1 (6.3)	1 (4.0)	0	0	NE	NE
Second GII.4[c]	Mild/Mod/Sev	1 (6.3)	1 (4.0)	0	0	NE	NE
Second GII (non-GII.4)[c]	Mod/Sev	0	1 (4.0)	0	1 (4.3)	NE	6 (-1410 to 94)
Second GII (non-GII.4)[c]	Mild	0	3 (12.0)	0	1 (4.3)	NE	-183 (-2624 to 71)
Second GII (non-GII.4)[c]	Mild/Mod/Sev	0	4 (16.0)	0	2 (8.7)	NE	-89 (-931 to 65)
First GI.1 or GII.4[a]	**Mild/Mod/Sev**	**39 (2.7)**	**70 (4.9)**	**43 (3.1)**	**63 (4.5)**	**11 (-38 to 42)**	**-9 (-53 to 23)**
First GII.4, N_3[a]	**Mild/Mod/Sev**	**39 (2.7)**	**70 (4.9)**	**43 (3.1)**	**63 (4.5)**	**11 (-38 to 42)**	**-9 (-53 to 23)**
Second GII.4[d]	Mod/Sev	0	0	1 (2.3)	1 (1.5)	NE	NE
Second GII.4[d]	Mild	2 (5.1)	2 (2.9)	1 (2.3)	1 (1.5)	-164 (-2816 to 76)	-101 (-2113 to 82)
Second GII.4[d]	Mild/Mod/Sev	2 (5.1)	2 (2.9)	2 (4.5)	2 (3.1)	-32 (-839 to 81)	0 (-612 to 86)
Second GII (non-GII.4)[d]	Mod/Sev	0	1 (1.4)	1 (2.3)	4 (6.2)	NE	75 (-124 to 97)
Second GII (non-GII.4)[d]	Mild	0	3 (4.3)	0	1 (1.5)	NE	-201 (-2793 to 69)
Second GII (non-GII.4)[d]	Mild/Mod/Sev	0	4 (5.8)	1 (2.3)	5 (7.7)	NE	20 (-199 to 78)
First GI or GII[a]	**Mod/Sev**	**43 (3.0)**	**80 (5.6)**	**51 (3.6)**	**85 (6.1)**	**17 (-25 to 45)**	**9 (-24 to 33)**
First GII[a]	**Mod/Sev**	**40 (2.8)**	**77 (5.4)**	**42 (3.0)**	**83 (5.9)**	**6 (-45 to 39)**	**8 (-26 to 32)**
First GII (non-GII.4), N_4[a]	**Mod/Sev**	**16 (1.1)**	**31 (2.2)**	**17 (1.2)**	**35 (2.5)**	**8 (-83 to 53)**	**14 (-40 to 47)**
Second GII.4[e]	Mod/Sev	0	1 (3.0)	0	1 (2.4)	NE	-21 (-1833 to 92)
Second GII.4[e]	Mild	0	0	0	0	NE	NE
Second GII.4[e]	Mild/Mod/Sev	0	1 (3.0)	0	1 (2.4)	NE	-21 (-1833 to 92)
Second GII (non-GII.4)[e]	Mod/Sev	0	2 (6.1)	0	1 (2.4)	NE	-142 (-2567 to 78)
Second GII (non-GII.4)[e]	Mild	0	0	0	0	NE	NE

Second GII (non-GII.4)[e]	Mild/Mod/Sev	0	2 (6.1)	0	1 (2.4)	NE	-142 (-2567 to 78)
First GI or GII[a]	**Mild**	**46 (3.2)**	**76 (5.3)**	**55 (3.9)**	**76 (5.4)**	**18 (-22 to 44)**	**2 (-34 to 29)**
First GII[a]	**Mild**	**28 (2.0)**	**64 (4.5)**	**42 (3.0)**	**61 (4.4)**	**31 (-12 to 57)**	**-4 (-47 to 27)**
First GII (non-GII.4), N_5[a]	**Mild**	**14 (1.0)**	**31 (2.2)**	**23 (1.6)**	**38 (2.7)**	**40 (-16 to 69)**	**20 (-28 to 50)**
Second GII.4[f]	Mod/Sev	0	0	0	1 (2.6)	NE	NE
Second GII.4[f]	Mild	1 (8.3)	1 (2.8)	2 (12.5)	2 (5.3)	15 (-838 to 92)	44 (-522 to 95)
Second GII.4[f]	Mild/Mod/Sev	1 (8.3)	1 (2.8)	0	3 (7.9)	NE	62 (-261 to 96)
Second GII (non-GII.4)[f]	Mod/Sev	1 (8.3)	1 (2.8)	0	1 (2.6)	NE	-13 (-1703 to 93)
Second GII (non-GII.4)[f]	Mild	0	3 (8.3)	0	1 (2.6)	NE	-238 (-3153 to 65)
Second GII (non-GII.4)[f]	Mild/Mod/Sev	1 (8.3)	4 (11.1)	0	2 (5.3)	NE	-351 (-3936 to 50)
First GI or GII[a]	**Mild/Mod/Sev**	**88 (6.2)**	**149 (10.4)**	**103 (7.4)**	**152 (10.9)**	**16 (-11 to 37)**	**5 (-19 to 24)**
First GII[a]	**Mild/Mod/Sev**	**68 (4.8)**	**141 (9.9)**	**42 (3.0)**	**144 (10.3)**	**18 (-13 to 41)**	**3 (-23 to 23)**
First GII (non-GII.4), N_6[a]	**Mild/Mod/Sev**	**29 (2.0)**	**60 (4.2)**	**39 (2.8)**	**80 (5.7)**	**27 (-18 to 55)**	**27 (-2 to 48)**
Second GII.4[g]	Mod/Sev	0	1 (1.4)	0	2 (2.5)	NE	42 (-545 to 95)
Second GII.4[g]	Mild	1 (3.4)	1 (1.4)	2 (12.5)	2 (2.5)	33 (-643 to 94)	42 (-545 to 95)
Second GII.4[g]	Mild/Mod/Sev	1 (3.4)	2 (2.9)	0	4 (5.1)	NE	42 (-219 to 89)
Second GII (non-GII.4)[g]	Mod/Sev	1 (3.4)	3 (4.3)	0	2 (2.5)	NE	-75 (-950 to 71)
Second GII (non-GII.4)[g]	Mild	0	3 (4.3)	0	1 (1.3)	NE	-251 (-3274 to 63)
Second GII (non-GII.4)[g]	Mild/Mod/Sev	1 (3.4)	6 (8.7)	0	3 (3.8)	NE	-134 (-835 to 41)

a. Percentage (%) = n/N.
b. Percentage (%) = n/N_1.
c. Percentage (%) = n/N_2.
d. Percentage (%) = n/N_3.
e. Percentage (%) = n/N_4.
f. Percentage (%) = n/N_5.
g. Percentage (%) = n/N_6.
h. Primary, secondary, and exploratory efficacy endpoint analyses (grey shaded rows): Vaccine efficacy is defined 100%[1– (λV/λC)], where λV and λC denote the hazard rates for the HIL-214 and Placebo arms respectively, obtained via a stratified Cox proportional hazards model, using Efron's method for handling ties. The model includes a term for vaccine arm and is stratified by country, whereby United States, Dominican Republic and Puerto Rico were considered one country. The 95% confidence interval is calculated by subtracting the confidence limits of hazard ratio from 1.
i. Post-hoc exploratory efficacy analyses (unshaded rows): Vaccine efficacy is defined 100%[1– (IRR), where IRR is the Incidence Rate Ratio, calculated as the exponent of the coefficient of the trial arm group in a Poisson regression model with log-transformed time to event variable and adjusted by country, whereby United States, Dominican Republic and Puerto Rico were considered one country. The 95% confidence interval of the IRR is also based on the Poisson distribution.

Abbreviations: AGE, acute gastroenteritis; GE, gastroenteritis; CI, confidence interval; mFAS, modified Full Analysis Set; NE, not estimable.

NOR-212: Safety

Table S7. Incidence of adverse events after any dose during the 6-month and ~16-month AGE surveillance periods in the NOR-212 study (SAF).

Adverse Event (AE) category, n (%)	Number of Participants, n (%)			
	HIL-214 (N=1541)		Placebo (N=1537)	
	6 mos AGE surveillance	~16 mos AGE surveillance	6 mos AGE surveillance	~16 mos AGE surveillance
Any AE[a]	938 (60.9)	944 (61.3)	937 (61.0)	945 (61.5)
Any solicited local reactions[b]	161 (10.4)	169 (11.0)	103 (6.7)	109 (7.1)
Any solicited systemic AE	581 (37.7)	614 (39.8)	540 (35.2)	560 (36.5)
Trial-vaccine related[b] solicited systemic AE	513 (33.3)	513 (33.3)	460 (29.9)	460 (29.9)
Any unsolicited systemic AE[c]	903 (58.6)	902 (58.5)	890 (57.9)	889 (57.9)
Any trial-vaccine related[b] unsolicited systemic AE	18 (1.2)	10 (0.6)	19 (1.2)	14 (0.9)
Any serious AE (SAE)[d]	145 (9.4)	169 (11.0)	132 (8.6)	165 (10.7)
Any trial-vaccine related[b] SAE	0	0	1 (<0.1)	1 (<0.1)
AE leading to trial vaccine discontinuation[d, e]	2 (0.1)	2 (0.1)	0	0
AE leading to trial discontinuation[d, e]	2 (0.1)	2 (0.1)	2 (0.1)	2 (0.1)
AE leading to death[d, e]	2 (0.1)	2 (0.1)	1 (<0.1)	1 (<0.1)

a. Includes only AEs collected in the AE form; for solicited local reactions and systemic AEs includes events which only occurred within 30 minutes of dosing.
b. Considered related if assessed as being possibly caused by the trial vaccine up to 7 days after vaccination.
c. As assessed up to 28 days after each vaccination.
d. As assessed throughout trial.
e. None were considered related to the trial vaccine.

Abbreviations: AE, adverse event; mos, months; SAE, serious adverse event; SAF, Safety Analysis Set.

NOR-212: Immunogenicity

Table S8. GI.1 and GII.4c-specific sNAbT (HBGA-blocking) and pan-Ig GMCs and GMFRs in participants who received HIL-214 or placebo in the NOR-212 study (FAS).

Antigen	Visit[a]	HIL-214 (N=1540)			Placebo (N=1537)		
		N_E	GMC (95% CI)	GMFR (95% CI)	N_E	GMC (95% CI)	GMFR (95% CI)
HBGA-blocking antibodies							
GI.1	Visit 1/Day 1	1538	21.0 (20.6-21.4)	–	1529	20.9 (20.5-21.3)	–
	Visit 2/Day 43	1446	60.8 (58.3-63.5)	2.9 (2.8-3.0)	1417	21.6 (21.0-22.1)	1.0 (1.0-1.0)
	Visit 3/Day 71	1415	421.2 (404.8-438.3)	20.1 (19.2-21.1)	1396	21.8 (21.2-22.4)	1.0 (1.0-1.1)
	Visit 4/Day 210	1392	165.7 (159.7-171.8)	7.9 (7.6-8.2)	1377	21.7 (21.1-22.3)	1.0 (1.0-1.1)
	Visit 5/Day 390	1248	100.1 (95.8-104.6)	4.8 (4.5-5.0)	1300	21.7 (21.2-22.2)	1.0 (1.0-1.1)
	Visit 6/Day 570	453	88.3 (82.1-94.9)	4.2 (3.9-4.5)	460	21.8 (20.9-22.8)	1.0 (1.0-1.1)
GII.4c	Visit 1/Day 1	1539	37.7 (37.0-38.4)	–	1529	39.2 (38.3-40.2)	–
	Visit 2/Day 43	1451	49.6 (47.8-51.4)	1.3 (1.3-1.4)	1417	39.8 (38.8-40.9)	1.0 (0.9-1.0)
	Visit 3/Day 71	1417	121.9 (115.8-128.2)	3.2 (3.1-3.4)	1396	41.0 (39.8-42.2)	1.0 (1.0-1.1)
	Visit 4/Day 210	1400	85.5 (81.4-89.7)	2.3 (2.2-2.4)	1377	45.6 (44.1-47.2)	1.2 (1.1-1.2)
	Visit 5/Day 390	60	111.0 (83.9-146.8)	3.0 (2.3-4.0)	72	51.7 (43.6-61.2)	1.4 (1.2-1.7)
	Visit 6/Day 570	0	–	–	0	–	–
Pan-Ig							
GI.1	Visit 1/Day 1	1536	116.3 (112.9-119.8)	–	1528	110.9 (107.9-114.0)	–
	Visit 2/Day 43	1450	1611.0 (1540.8-1684.5)	13.9 (13.1-14.7)	1417	95.9 (93.6-98.4)	0.9 (0.8-0.9)
	Visit 3/Day 71	1416	10419.5 (10031.8-10822.2)	89.9 (85.2-94.7)	1397	95.4 (92.5-98.4)	0.9 (0.8-0.9)
	Visit 4/Day 210	1399	3653.7 (3522.2-3790.1)	31.4 (29.9-33.0)	1378	118.3 (113.3-123.6)	1.1 (1.0-1.1)
	Visit 5/Day 390	825	1667.1 (1594.3-1743.2)	14.1 (13.3-15.0)	1029	147.5 (139.2-156.2)	1.3 (1.2-1.4)
	Visit 6/Day 570	331	1631.0 (1524.7-1744.7)	14.6 (13.2-16.2)	373	152.7 (139.0-167.8)	1.5 (1.3-1.6)
GII.4c	Visit 1/Day 1	1536	111.8 (107.1-116.8)	–	1528	114.7 (109.5-120.0)	–
	Visit 2/Day 43	1451	321.4 (302.5-341.5)	2.9 (2.7-3.1)	1416	99.6 (94.5-105.0)	0.9 (0.8-0.9)
	Visit 3/Day 71	1418	1652.8 (1564.0-1746.7)	14.8 (13.8-15.8)	1397	105.3 (99.2-111.8)	0.9 (0.9-1.0)
	Visit 4/Day 210	1401	1081.0 (1020.4-1145.2)	9.6 (9.0-10.3)	1378	178.0 (164.1-193.1)	1.6 (1.4-1.7)
	Visit 5/Day 390	813	499.9 (468.6-533.3)	4.8 (4.4-5.2)	905	171.8 (158.5-186.3)	1.6 (1.5-1.7)
	Visit 6/Day 570	276	501.9 (450.8-558.7)	4.8 (4.1-5.6)	303	230.4 (199.4-266.2)	2.2 (1.9-2.6)

a. Fewer HIL-214 and placebo recipients were tested beyond Visit 4 following early trial termination by the sponsor.

Abbreviations: N_E, number of participants with evaluable samples; CI, confidence interval; GMC, geometric mean concentration; GMFR, geometric mean fold-rise; HBGA, histo-blood group antigen (where HBGA refers to HBGA-blocking antibody under Ab type).

Table S9. Seroresponse rates (SRRs) of GI.1 and GII.4c-specific HBGA-blocking antibodies (sNAb) in participants who received HIL-214 or placebo in the NOR-212 study (FAS).

	Visit[b]	GI.1		GII.4c	
		HIL-214 (N=1540)	Placebo (N=1537)	HIL-214 (N=1540)	Placebo (N=1537)
HBGA seroresponse rate, n/N_E (%)[a]					
	Visit 2/Day 43	532/1445 (36.8)	9/1412 (0.6)	108/1450 (7.4)	19/1412 (1.3)
	Visit 3/Day 71	1351/1414 (95.5)	19/1390 (1.4)	609/1416 (43.0)	31/1390 (2.2)
	Visit 4/Day 210	1199/1391 (86.2)	22/1371 (1.6)	350/1399 (25.0)	85/1371 (6.2)
	Visit 5/Day 390	745/1247 (59.7)	19/1293 (1.5)	21/60 (35.0)	10/72 (13.9)
	Visit 6/Day 570	251/453 (55.4)	9/459 (2.0)	NT	NT
Pan-Ig seroresponse rate, n/N_E (%)[a]					
	Visit 2/Day 43	1224/1447 (84.6)	19/1411 (1.3)	549/1448 (37.9)	47/1410 (3.3)
	Visit 3/Day 71	1399/1414 (98.9)	33/1390 (2.4)	118/1416 (83.9)	113/1390 (8.1)
	Visit 4/Day 210	1356/1397 (97.1)	119/1371 (8.7)	1055/1398 (75.5)	324/1371 (23.6)
	Visit 5/Day 390	747/823 (90.8)	143/1021 (14.0)	494/810 (61.0)	228/898 (25.4)
	Visit 6/Day 570	310/331 (93.7)	60/372 (16.1)	170/275 (61.8)	108/303 (35.6)

a. Percentage (%) = n/N_E.

b. Fewer HIL-214 and placebo recipients were tested beyond Visit 4 following early trial termination by the sponsor.

Abbreviations: FAS, Full Analysis Set; N_E, number of participants with evaluable samples; NT, not tested; SRR, seroresponse rate

NOR-212: Breadth of GII.4 immune responses following vaccination and GII.4 associated AGE

Table S10. Summary of participants included and excluded from GII.4 sNAb breadth analyses, stratified by variant and severity, among those with a first GII.4-associated AGE event during the 6-month AGE surveillance period in the NOR-212 study.

Norovirus genotypes or genogroups	AGE symptom severity	6 mos AGE surveillance			
		Included		Excluded	
		(AGE >Visit 3 <Visit 4)/ Total Observed[a, b]		(AGE >Visit 4, GII.4 sNAbT <Visit 3, or No sample)/Total Observed[c]	
		HIL-214	Placebo	HIL-214	Placebo
Any GII.4, n/N (%)	**Mod/Sev**	**16/23 (70%)**	**12/26 (46%)**	**7/23 (30%)**	**14/26 (54%)**
GII.4_SF	Mod/Sev	5/7	5/12	2/7	7/12
GII.4_SY	Mod/Sev	7/8	6/10	1/8	4/10
GII.4_WI	Mod/Sev	4/7	0/2	3/7	2/2
GII.4_AL	Mod/Sev	0	0	0	0
GII.4_N/A	Mod/Sev	0/1	1/2	1/1	1/2
Any GII.4, n/N (%)	**Mild**	**10/16 (63%)**	**12/18 (67%)**	**6/16 (38%)**	**6/18 (33%)**
GII.4_SF	Mild	8/12	6/10	4/12	4/10
GII.4_SY	Mild	1/1	4/4	0/1	0/4
GII.4 _WI	Mild	1/1	2/3	0/1	1/3
GII.4_AL	Mild	0/1	0/1	1/1	1/1
GII.4_N/A	Mild	0/1	0	1/1	0
Any GII.4, n/N (%)	**Mild/Mod/Sev**	**26/39 (67%)**	**24/44 (55%)**	**13/39 (33%)**	**20/44 (45%)**
GII.4_SF	Mild/Mod/Sev	13/19	11/22	6/19	11/22
GII.4_SY	Mild/Mod/Sev	8/9	10/14	1/9	4/14
GII.4_WI	Mild/Mod/Sev	5/8	2/5	3/8	3/5
GII.4_AL	Mild/Mod/Sev	0/1	0/1	1/1	1/1
GII.4_N/A	Mild/Mod/Sev	0/2	1/2	2/2	1/2

a. Among the 39 HIL-214 recipients that experienced a GII.4-associated AGE event of any severity through 6-months AGE surveillance, 28 of 39 (71.8%) occurred after Visit 3 and before Visit 4 (16 mod/sev, 12 mild) and 26 of 28 (92.9%) had serum available for GII.4 sNAbT breadth evaluation.

b. Among the 44 placebo recipients that experienced a GII.4-associated AGE event of any severity through 6-months AGE surveillance, 29 of 44 (65.9%) occurred after Visit 3 and before Visit 4 (16 mod/sev, 13 mild) and 24 of 29 (82.7%) had serum available for analysis.

c. HIL-214 and placebo recipients that experienced a symptomatic GII.4-associated AGE event after Visit 4 but before 6-months AGE surveillance or asymptomatic GII.4 infection before Visit 3 with observable sNAbT were excluded from sNAbT breadth evaluation

Table S11. Summary of demographic characteristics of participants evaluated for GII.4 sNAb breadth during the 6-month AGE surveillance period in the NOR-212 study.

Category	Number of participants, n (%)					
	HIL-214			Placebo		
		Included (>Visit 3 <Visit 4)			Included (>Visit 3 <Visit 4)	
	FAS (N=1540)	GI/GII AGE- (N=25)[a]	Mild/Mod/Sev GII.4 AGE+ (N=26)[b, c]	FAS (N=1538)	GI/GII AGE- (N=20)[a]	Mild/Mod/Sev GII.4 AGE+ (N=24)[b, d]
Age, months						
Mean (SD)	5.0	5.0	4.9	4.9	5.1	5.0
Gender, n (%)						
Male	763 (50)	14 (44)	14 (56)	738 (48)	12 (60)	10 (42)
Ethnicity, n (%)						
Hispanic or Latino	1521 (99)	25 (100)	25 (96)	1520 (99)	20 (100)	24 (100)
Unknown	14 (<1)	0	0	14 (<1)	0	0
Not Hispanic or Latino	5 (<1)	0	1 (4)	4 (<1)	0	0
Race, n (%)						
Other	1429 (93)	24 (96)	26 (100)	1429 (93)	18 (90)	19 (79)
Not Reported	72 (5)	1 (4)	0	61 (4)	2 (10)	2 (8)
Unknown	15 (1)	0	0	16 (1)	0	0
Black or African American	10 (<1)	0	0	14 (<1)	0	2 (8)
Multiracial	10 (<1)	0	0	12 (<1)	0	1 (4)
White	3 (<1)	0	0	5 (<1)	0	0
American Indian or Alaska Native	0	0	0	1 (<0.1)	0	0
Asian	1 (<0.1)	0	0	0	0	0
Country, n (%)						
Panama	818 (53)	11 (4)	18 (69)	817 (53)	7 (35)	15 (63)
Dominican Republic	310 (20)	10 (40)	0	308 (20)	9 (45)	1 (4)
Honduras	260 (17)	2 (8)	6 (23)	260 (17)	1 (5)	4 (17)
Peru	105 (7)	1 (4)	2 (8)	105 (7)	2 (10)	0
Colombia	43 (3)	1 (4)	0	44 (3)	1 (5)	4 (17)
Puerto Rico	3 (<1)	0	0	3 (<1)	0	0
United States of America	1 (<0.1)	0	0	1 (<0.1)	0	0

a. Participants selected for the HIL-214 GI/GII AGE- (N=25) and placebo GI/GII AGE- (N=20) subsets included those who did not experience a GI or GII AGE event (including GII.4) of any severity during the 6-months AGE surveillance period and had no observable GII.4 sNAbT before Visit 5

b. Participants selected for the HIL-214 GII.4 AGE+ (N=26) and placebo GII.4 AGE+ (N=24) subsets included those who experienced a GII.4 AGE event of any severity during the 6-months AGE surveillance period between Visit 3 and Visit 4 (12 mos of age), excluding those who had a GII.4 AGE event after Visit 4 but before primary analysis (~13 mos of age) or had an observable GII.4 sNAbT at Visit 3. Full distribution of all GII.4 AGE+ cases (and cases selected for GII.4 sNAbT breadth analyses) by GII.4 variant, severity, country, and treatment arm is shown in **Table S5**

c. Among the 39 HIL-214 recipients that experienced a GII.4-associated AGE event of any severity through 6-months AGE surveillance, 28 of 39 (71.8%) occurred after Visit 3 and before Visit 4 (16 mod/sev, 12 mild) and 26 of 28 (92.9%) had serum available for GII.4 sNAbT breadth evaluation.

d. Among the 44 placebo recipients that experienced a GII.4-associated AGE event of any severity through 6-months AGE surveillance, 29 of 44 (65.9%) occurred after Visit 3 and before Visit 4 (16 mod/sev, 13 mild) and 24 of 29 (82.7%) had serum available for GII.4 sNAbT breadth evaluation.

Abbreviations: AGE, acute gastroenteritis; FAS, Full Analysis Set.

Table S12. Association between GII.4 AGE severity (mild vs. mod/sev) and GII.4 variant specific sNAbT at Visit 4 in HIL-214 and placebo recipients (NOR-212). Stratified linear regression predicting Visit 4 GII.4 sNAbT to variants adjusted for AGE severity among HIL-214 and placebo recipients with confirmed GII.4 AGE+ events between Visits 3 and 4 (**see Tables S5, S10, and S11**). Δ AGE sNAbT represents the GMT difference (linear) in GII.4 sNAbT for mod/severe GII.4 AGE compared to mild GII.4 AGE.

	HIL-214 (N=26)						Placebo (N=24)					
	β	SE	95% CI		X^2	*P* value[a]	β	SE	95% CI		X^2	*P* value[b]
			LL	UL					LL	UL		
GII.4c												
Δ AGE sNAbT	3215.8	2533.5	-1749.9	8181.4	1.61	0.2043	300.0	286.4	-261.4	861.4	1.10	0.2949
GII.4_SF												
Δ AGE sNAbT	-317.8	287.1	-880.4	244.9	1.20	0.2738	1024.5	887.7	-715.4	2764.3	1.30	0.2549
GII.4_SY												
Δ AGE sNAbT	1886.7	1206.4	-477.9	4251.3	2.34	0.1263	2132.2	1654.1	-1109.8	5374.3	1.61	0.2050
GII.4_WI												
Δ AGE sNAbT	595.9	343.9	-78.2	1270.0	2.84	0.0919	139.6	332.2	-511.6	790.7	0.18	0.6750
GII.4_AL												
Δ AGE sNAbT	394.2	199.9	2.4	786.0	3.62	0.0569	677.4	611.5	-521.1	1876.0	1.20	0.2739

a. *P*-value model statistics are shown for the overall model (two-sided tests). Models with mild vs moderate vs severe were fitted and significance of difference in GII.4 sNAbT between AGE severity subsets found no statistically significant association with GII.4 sNAbT at Visit 4.

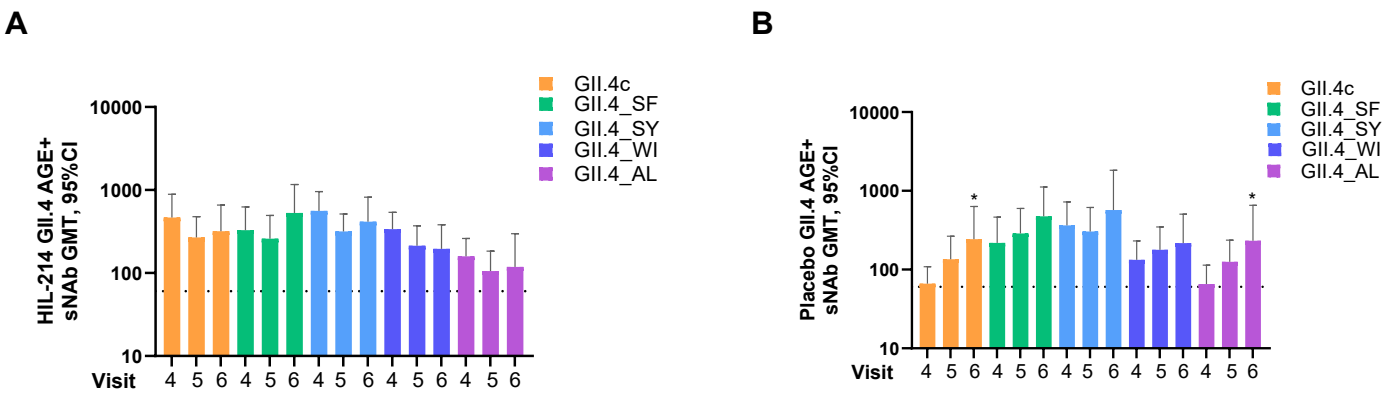
Abbreviations: β, standardized regression coefficient; sNAbT, surrogate neutralizing antibody titer; SE, standard error; 95% CI LL, lower limit of the 95% confidence interval; 95% CI UL, upper limit of the 95% confidence interval.

Table S13. GII.4 variant-specific sNAbT at Visit 4 stratified by severity of first GII.4 AGE event and infecting GII.4 variant in HIL-214 and placebo recipients between Visits 3 and 4 (NOR-212).

GII.4 Variant	GII.4 sNAbT by AGE Severity	HIL-214			Placebo		
		Mild	Mod/Sev		Mild	Mod/Sev	
		GMT (95% CI)	GMT (95% CI)	X^2 (*P* value)[a]	GMT (95% CI)	GMT (95% CI)	X^2 (*P* value)[a]
GII.4_SF		**N=8**	**N=5**		**N=6**	**N=5**	
	GII.4c sNAb	216.6 98.6-475.9	430.5 39.1-4741.2	3.53 (0.0872)	34.4 24.2-49.1	30.0 30.0-30.0	0.82 (0.3893)
	GII.4_SF sNAb	1053.1 687.5-1613.1	1022.4 451.8-2313.4	0.01 (0.9104)	649.6 264.4-1596.1	1087.2 676.3-1747.9	1.45 (0.2595)
	GII.4_SY sNAb	224.5 128.2-393.2	303.7 58.8-1568.9	1.59 (0.2337)	65.9 33.2-130.8	133.6 55.6-321.0	3.18 (0.1080)
	GII.4_WI sNAb	215.3 127.9-362.6	303.5 125.5-734.1	1.33 (0.2736)	107.3 48.9-235.8	154.5 102.8-232.2	0.78 (0.3992)
	GII.4_AL sNAb	72.7 35.1-150.5	140.9 22.1-897.5	2.61 (0.1342)	34.3 24.3-48.3	30.0 30.0-30.0	0.82 (0.3893)
GII.4_SY		**N=1**	**N=7**		**N=4**	**N=6**	
	GII.4c sNAb	153.4	1113.5 200.8-6176.4	0.18 (0.6846)	97.8 18.4-518.5	157.7 24.4-1019.3	0.57 (0.4700)
	GII.4_SF sNAb	30.0	155.9 38.3-634.9	0.29 (0.6076)	45.7 12.0-174.3	123.5 10.8-1414.9	0.64 (0.4460)
	GII.4_SY sNAb	605.5	2030.5 716.1-5757.5	0.28 (0.6159)	925.7 277.5-3088.6	2063.4 483.4-8807.6	0.86 (0.3800)
	GII.4_WI sNAb	30.0	259.1 108.7-617.9	0.75 (0.4212)	44.6 12.6-157.0	151.7 21.6-1066.6	0.78 (0.4025)
	GII.4_AL sNAb	60.9	320.2 108.0-949.5	0.40 (0.5501)	59.7 14.0-254.1	230.2 29.2-1813.0	0.74 (0.4153)
GII.4_WI		**N=1**	**N=4**		**N=2**	**N=0**	
	GII.4c sNAb	98.0	998.1 97.6-10208.8	0.32 (0.6123)	74.9 8.7-647.7	-	NE
	GII.4_SF sNAb	30.0	95.4 7.8-1162.6	0.26 (0.6476)	30.0 30.0-30.0	-	NE
	GII.4_SY sNAb	200.3	1014.5 212.9-4833.1	0.67 (0.4741)	418.5 99.4-1763.2	-	NE
	GII.4_WI sNAb	853.3	2192.8 1017.9-4723.7	1.18 (0.3573)	1375.1 809.8-2335.3	-	NE
	GII.4_AL sNAb	149.1	341.0 62.8-1851.5	0.26 (0.6453)	73.3 0.0-6268166.1	-	NE
GII.4_AL		**N=0**	**N=0**		**N=0**	**N=0**	
	GII.4c sNAb	-	-		-	-	
	GII.4_SF sNAb	-	-		-	-	
	GII.4_SY sNAb	-	-		-	-	
	GII.4_WI sNAb	-	-		-	-	
	GII.4_AL sNAb	-	-		-	-	
GII.4_N/A		**N=0**	**N=0**		**N=0**	**N=1**	
	GII.4c sNAb	-	-		-	165.2	NE
	GII.4_SF sNAb	-	-		-	85.2	NE
	GII.4_SY sNAb	-	-		-	895.4	NE
	GII.4_WI sNAb	-	-		-	81.1	NE
	GII.4_AL sNAb	-	-		-	94.3	NE

a. X^2, group comparisons performed using ANOVA with Tukey's HSD, corresponding P-values are shown.

Abbreviations: AGE, acute gastroenteritis; CI, confidence interval; GMT, geometric mean titers; NE, not estimable; sNAbT, surrogate neutralizing antibody titers; -, indicates that no samples were tested in that grouping.



231

232 **Figure S2. GII.4 sNAbT breadth at Visits 4-6 in participants who experienced a first GII.4-associated AGE**
233 **event between Visits 3 and Visit 4 in the NOR-212 study.** GMT (95% CI) of GII.4 sNAbT at Visit 4/Day 210 (1
234 year of age), Visit 5/Day 390 (18 months of age), and Visit 6/Day 570 (2 years of age). **(A)** HIL-214 GII.4 AGE+
235 (N=26) and **(B)** Placebo GII.4 AGE+ (N=24) participants. Dotted lines, limit of detection. *, P < 0.02 compared to
236 Visit 4/Day 210, Mann-Whittney test.

237

Table S14. Proportion of HIL-214 (aged 0.4, 0.5-<1, 1-<4, and 18<50 yrs) and placebo (aged 0.4 yrs) recipients achieving ≥4-fold increase in GII.4 sNAbT to between 0 and 5 variants, stratified by study, age group, and pre-vaccination GII.4 status (NOR-212, NOR-202, NOR-215). These data represent the GII.4 sNAbT breadth rate visualized in Figures 3H, 5I, and S5.

Data represented as percentages in Figure 3H (NOR-212)									
n/N (%)			Number of GII.4 Variants						Total
			0	1	2	3	4	5	
Visit 3	AGE	HIL-214	16 (61.5)	10 (38.5)	0 (0)	0 (0)	0 (0)	0 (0)	26
		Placebo	24 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	24
	No AGE	HIL-214	12 (48.0)	13 (52.0)	0 (0)	0 (0)	0 (0)	0 (0)	25
		Placebo	20 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	20
Visit 4	AGE	HIL-214	0 (0)	8 (30.8)	3 (11.5)	6 (23.1)	4 (15.4)	5 (19.2)	26
		Placebo	1 (4.2)	16 (66.7)	5 (20.8)	1 (4.2)	0 (0)	1 (4.2)	24
	No AGE	HIL-214	25 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	25
		Placebo	20 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	20

Data represented as percentages in Figure 5I (NOR-212, NOR-202, NOR-215)							
n/N (%)	Number of GII.4 Variants						Total
	0	1	2	3	4	5	
Pre-Vx GII.4 seronegative 0.4 yrs	25 (53.2)	22 (46.8)	0 (0)	0 (0)	0 (0)	0 (0)	47
Pre-Vx GII.4 seropositive 0.4 yrs	3 (75.0)	1 (25.0)	0 (0)	0 (0)	0 (0)	0 (0)	4
Pre-Vx GII.4 seronegative 0.5-<1 yrs	11 (78.6)	3 (21.4)	0 (0)	0 (0)	0 (0)	0 (0)	14
Pre-Vx GII.4 seropositive 0.5-<1 yrs	1 (50.0)	0 (0)	0 (0)	0 (0)	1 (50.0)	0 (0)	2
Pre-Vx GII.4 seronegative 1-<4 yrs	19 (79.2)	5 (20.8)	0 (0)	0 (0)	0 (0)	0 (0)	24
Pre-Vx GII.4 seropositive 1-<4 yrs	1 (1.5)	1 (1.5)	2 (3.0)	1 (1.5)	6 (9.0)	56 (83.6)	67
Pre-Vx GII.4 seronegative 4-<9 yrs	2 (66.7)	1 (33.3)	0 (0)	0 (0)	0 (0)	0 (0)	3
Pre-Vx GII.4 seropositive 4-<9 yrs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	21 (100)	21
Pre-Vx GII.4 seronegative 18-<50 yrs	11 (52.4)	7 (33.3)	0 (0)	0 (0)	1 (4.8)	2 (9.5)	21
Pre-Vx GII.4 seropositive 18-<50 yrs	0 (0)	2 (3.6)	2 (3.6)	6 (10.7)	27 (48.2)	19 (33.9)	56

Data represented as percentages in Figure S5 by ICH E11 age group (NOR-212, NOR-202, NOR-215)							
n/N (%)	Number of GII.4 Variants						Total
	0	**1**	**2**	**3**	**4**	**5**	
Pre-Vx GII.4 seronegative 0.4 yrs	25 (53.2)	22 (46.8)	0 (0)	0 (0)	0 (0)	0 (0)	47
Pre-Vx GII.4 seropositive 0.4 yrs	3 (75.0)	1 (25.0)	0 (0)	0 (0)	0 (0)	0 (0)	4
Pre-Vx GII.4 seronegative 0.5-<1 yrs	11 (78.6)	3 (21.4)	0 (0)	0 (0)	0 (0)	0 (0)	14
Pre-Vx GII.4 seropositive 0.5-<1 yrs	1 (50.0)	0 (0)	0 (0)	0 (0)	1 (50.0)	0 (0)	2
Pre-Vx GII.4 seronegative 1-<2 yrs	6 (85.7)	1 (14.3)	0 (0)	0 (0)	0 (0)	0 (0)	7
Pre-Vx GII.4 seropositive 1-<2 yrs	0 (0)	1 (7.7)	0 (0)	1 (7.7)	4 (33.8)	7 (53.8)	13
Pre-Vx GII.4 seronegative 2-<9 yrs	15 (75.0)	5 (25.0)	0 (0)	0 (0)	0 (0)	0 (0)	20
Pre-Vx GII.4 seropositive 2-<9 yrs	1 (1.3)	0 (0)	2 (2.7)	0 (0)	2 (2.7)	70 (93.3)	75
Pre-Vx GII.4 seronegative 18-<50 yrs	11 (52.4)	7 (33.3)	0 (0)	0 (0)	1 (4.8)	2 (9.5)	21
Pre-Vx GII.4 seropositive 18-<50 yrs	0 (0)	2 (3.6)	2 (3.6)	6 (10.7)	27 (48.2)	19 (33.9)	56

Nonclinical: Sequential immunization of GII.4 naïve mice with divergent GII.4 variants improves breadth

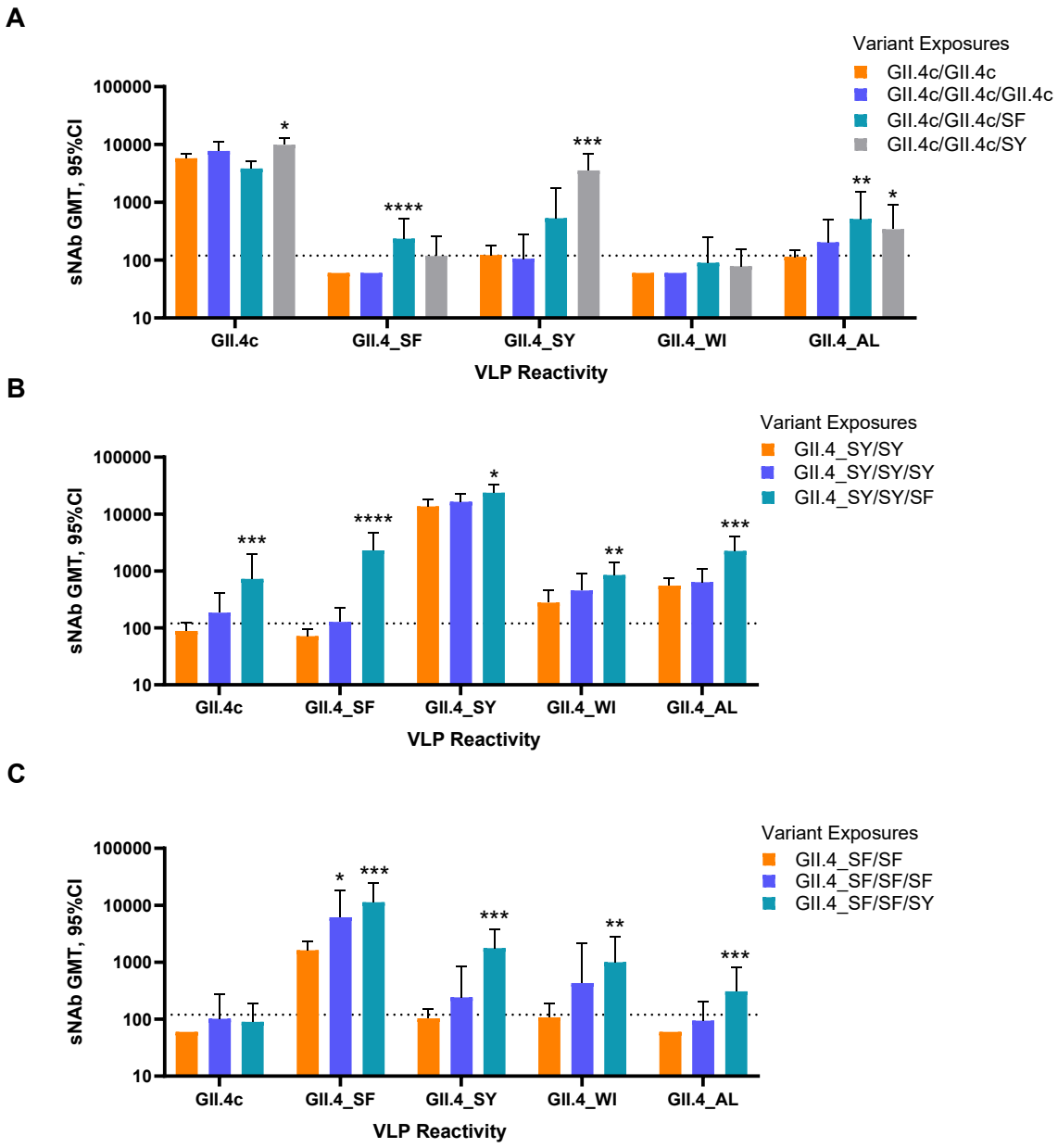


Figure S3. GII.4 sNAb responses against heterologous variants following single or combined GII.4 variant VLP immunization in human norovirus-naïve mice. Mice were immunized with a single VLP at weeks 0 and 4 and received either a third dose of the same VLP or a single dose of a different GII.4 variant at week 8. Terminal bleeds were collected at week 12. sNAb GMT for vaccines with **(A)** GII.4c, **(B)** GII.4_SY, or **(C)** GII.4_SF as the first and second immunogen. *, $P < 0.05$; **, $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$ Dunn's test. Dashed line, limit of detection.

NOR-202: Patient disposition and demographics among HIL-214 vaccinated children (0.4-<9 yrs) tested for GII.4 sNAbT breadth

Table S15. Summary of demographic characteristics of children evaluated for GII.4 sNAb breadth by pre-specified and post-hoc defined age groups among recipients of single dose of a HIL-214 (15/15, 15/50, 50/50, 50/150 μg) in the NOR-202 study.

Age Group	Number of participants, n/N (%)																							
	Combined Formulations | Compositions (15/15 | 15/50 | 50/50 | 50/150 μg)[a, b]																							
	Group 1 (4-<9 yr)				4-<5 yr				5-<6 yr				6-<7 yr				7-<8 yr				8-<9 yr			
Total n/N, (%)	**24/108 (22)**				11				3				6				4				0			
	27	**29**	**26**	**26**	0	2	4	5	0	2	1	0	0	3	2	1	0	1	0	3	0	0	0	0
Age, mean, n (yr)	**5.9**				4.7				5.7				6.7				7.5				0			
	5.7	**5.8**	**6.1**	**5.8**	0	4.8	4.6	4.7	0	5.6	5.9	0	0	6.7	6.7	6.5	0	7.5	0	7.4	0	0	0	0
Gender, male, n/N (%)	**11/52 (21)**				2				3				4				3				0			
	16	**12**	**11**	**13**	0	1	0	1	0	2	1	0	0	2	1	1	0	0	0	2	0	0	0	0
Race, n/N (%)																								
White	**0/58 (0)**				0				0				0				0				0			
	15	**16**	**14**	**13**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
American Indian or Alaska Native	**15/37 (41)**				6				3				5				1				0			
	9	**10**	**10**	**8**	0	1	3	2	0	2	1	0	0	2	2	1	0	0	0	1	0	0	0	0
Asian	**0**				0				0				0				0				0			
	0	**0**	**0**	**0**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Black or African American	**2/3 (67)**				1				0				0				1				0			
	1	**0**	**0**	**2**	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
Native Hawaiian or Pacific Islander	**0**				0				0				0				0				0			
	0	**0**	**0**	**0**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Multiracial	**0**				0				0				0				0				0			
	0	**0**	**0**	**0**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Other	**7/10 (70)**				4				0				1				2				0			
	2	**3**	**2**	**3**	0	1	1	2	0	0	0	0	0	1	0	0	0	1	0	1	0	0	0	0
Ethnicity, n/N (%)																								
Hispanic or Latino	**24/50 (48)**				11				3				6				4				0			
	12	**13**	**12**	**13**	0	2	4	5	0	2	1	0	0	3	2	1	0	1	0	3	0	0	0	0
Not reported	**0**				0				0				0				0				0			
	0	**0**	**0**	**0**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Country, n/N (%)																								
Finland	**0/66 (0)**				0				0				0				0				0			
	16	**17**	**17**	**16**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Colombia	**7/10 (70)**				4				0				1				2				0			
	2	**3**	**2**	**3**	0	1	1	2	0	0	0	0	0	1	0	0	0	1	0	1	0	0	0	0
Panama	**17/44 (39)**				7				3				5				2				0			
	11	**10**	**11**	**12**	0	1	3	3	0	2	1	0	0	2	2	1	0	0	0	2	0	0	0	0

Age Group	Combined Formulations | Compositions (15/15 | 15/50 | 50/50 | 50/150 µg)[a, b]																							
	Group 2/2a (1-<4 yr)				**1-<2 yr**				**2-<3 yr**				**3-<4 yr**				**Group 3 (6-<12) mo**				**0.5-<1 yr**			
n/N, (%)	**91/220 (41)**				20				47				24				**16/108 (15)**				16			
	54	**58**	**52**	**56**	0	8	10	2	0	14	12	21	0	12	8	4	**27**	**25**	**27**	**29**	0	6	6	4
Age, mean, n (yr)	**2.1**				1.6				2.5				3.5				**0.7**				0.7			
	2.0	**2.2**	**1.9**	**2.1**	0	1.5	1.5	1.8	0	2.5	2.4	2.5	0	3.5	3.5	3.5	**0.6**	**0.7**	**0.7**	**0.7**	0	0.7	0.7	0.7
Gender, male, n/N (%)	**53/123 (43)**				13				29				11				**6/57 (11)**				6			
	30	**28**	**31**	**34**	0	5	6	2	0	8	9	12	0	3	5	3	**17**	**11**	**14**	**15**	0	2	1	2
Race, n/N (%)																								
White	**2/57 (4)**				0				2				0				**0/2 (0)**				0			
	14	**14**	**12**	**17**	0	0	0	0	0	1	0	1	0	0	0	0	**1**	**0**	**0**	**1**	0	0	0	0
American Indian or Alaska Native	**22/39 (56)**				6				12				4				**6/53 (11)**				6			
	11	**10**	**9**	**9**	0	2	4	0	0	4	2	6	0	2	1	1	**13**	**15**	**11**	**14**	0	3	2	1
Asian	**0**				0				0				0				**0/1 (0)**				0			
	0	**0**	**0**	**0**	0	0	0	0	0	0	0	0	0	0	0	0	***0***	***0***	***1***	***0***	0	0	0	0
Black or African American	**12/18 (67)**				4				4				4				**2/12 (17)**				2			
	3	**4**	**8**	**3**	0	1	2	1	0	1	2	1	0	1	2	1	**3**	**2**	**4**	**3**	0	1	1	0
Native Hawaiian or Pacific Islander	**0**				0				0				0				**0/1 (0)**				0			
	0	**0**	**0**	**0**	0	0	0	0	0	0	0	0	0	0	0	0	**1**	**0**	**0**	**0**	0	0	0	0
Multiracial	**0/2 (0)**				0				0				0				**0**				0			
	0	**2**	**0**	**0**	0	0	0	0	0	0	0	0	0	0	0	0	**0**	**0**	**0**	**0**	0	0	0	0
Other	**55/104 (53)**				10				29				16				**8/39 (21)**				8			
	26	**28**	**23**	**27**	0	5	4	1	0	8	8	13	0	9	5	2	**9**	**8**	**11**	**11**	0	2	3	3
Ethnicity, n/N (%)																								
Hispanic or Latino	**91/163 (56)**				20				47				24				**16/108 (15)**				16			
	40	**43**	**40**	**40**	0	8	10	2	0	14	12	21	0	12	8	4	**27**	**25**	**27**	**29**	0	6	6	4
Not reported	**0/2 (0)**				0				0				0				**0**				0			
	0	**0**	**0**	**2**	0	0	0	0	0	0	0	0	0	0	0	0	**0**	**0**	**0**	**0**	0	0	0	0
Country, n/N (%)																								
Finland	**0/62 (0)**				0				0				0				**0**				0			
	16	**15**	**15**	**16**	0	0	0	0	0	0	0	0	0	0	0	0	**0**	**0**	**0**	**0**	0	0	0	0
Colombia	**63/129 (49)**				12				32				19				**7/48 (15)**				7			
	33	**32**	**31**	**33**	0	5	5	2	0	8	9	15	0	10	7	2	**12**	**12**	**12**	**12**	0	3	3	3
Panama	**28/49 (57)**				8				15				5				**9/72 (13)**				9			
	12	**13**	**13**	**11**	0	3	5	0	0	6	3	6	0	2	1	2	**18**	**18**	**18**	**18**	0	3	3	1

a. Subjects recruited in Finland were allocated only to Group 1 (4–<9 y) and Group 2 (1–<4 y). Subjects recruited in Colombia and Panama were allocated to Group 2a (1–<4 y), Group 3 (6–<12 mos) and Group 4 (6 wk–<6 mos), in addition to Group 1 and Group 2. Sources: 1 - <9 yrs[2], 6 mos – <4 yrs[3], 6 wks – <6 mos[4]

b. Young infants (Group 4, 6 wks–<6 mos) and recipients of the 15/15 µg antigen composition were excluded from GII.4 sNAbT breadth analyses; within each age group, the remaining antigen compositions (15/50, 50/50, and 50/150 µg) were combined. See Methods for details.

NOR-215: Patient disposition and demographics among HIL-214 vaccinated adults tested for GII.4 sNAbT breadth

Table S16. Summary of demographic characteristics of adults evaluated for GII.4 sNAb breadth among recipients of a single dose of a HIL-214 (50/150 μg) in the NOR-215 study[5].

	Number of participants, n/N (%)
Age Group	**Composition (50/150 μg)/Single-Dose**
	18-<50 yrs
Total n/N, (%)	**77/80 (96%)**
Age, mean, (yr)	35.2
Gender, male, n/n (%)	31/32 (97)
Race, n/N (%)	
White	28/31 (90)
American Indian or Alaska Native	1/1 (100)
Asian	5/5 (100)
Black or African American	40/40 (100)
Native Hawaiian or Pacific Islander	0
Multiracial	2/2 (100)
Other	1/1 (100)
Ethnicity, n/N (%)	
Hispanic or Latino	16/17 (94)
Not Hispanic or Latino	61/63 (97)
Country, n/N (%)	
United States	77/80 (96)

NOR-202/NOR-215: HIL-214 boosts GII.4 sNAbT breadth in older children and adults exposed to contemporary GII.4_SY variants

Table S17. GII.4 sNAb GMT (95% CI) in infants, toddlers, and children aged 0.5-<9 years in the NOR-202 study and adults aged 18-<50 years in the NOR-215 study. Sera were collected pre-vaccination (Pre-Vx) and 28 days post-dose 1 vaccination (Post-Vx) with HIL-214 (for NOR-202 combined formulations/compositions groups, see **Table S15**). Bolded values represent significant difference of sNAbT from pre-vaccination values for the same GII.4 variant (Mann-Whitney test).

	NOR-202									NOR-215		
	HIL-214 (1 dose of 15/50, 50/50, or 50/150 µg; combined)									1x 50/150 µg		
Age Group	**0.5-<1 yr (N=16)**	**1-<2 yr (N=20)**	**2-<3 yr (N=47)**	**3-<4 yr (N=24)**	**4-<5 yr (N=11)**	**5-<6 yr (N=3)**	**6-<7 yr (N=6)**	**7-<8 yr (N=4)**	**8-<9 yr (N=0)**	**1-<4 yr (N=91)**	**4-<9yr (N=24)**	**18-<50 yr (N=77)**
GII.4 sNAb, GMT (95% CI)												
GII.4c												
Pre-Vx	33.7 (26.3-43.28)	125.9 (66.8-237.5)	135.7 (91.4-201.5)	158.6 (78.7-319.7)	480.5 (259.5-889.5)	116.8 (26.1-523.6)	169.7 (62.8-458.4)	81.0 (12.3-533.0)	—	139.1 (103.4-187.1)	230.7 (142.3-373.9)	171.8 (125.8-234.5)
Post-Vx	**94.0 (54.0-163.6) *P*=0.0004**	**443.2 (201.1-976.4) *P*=0.0134**	**1931 (1137-3278) *P*<0.0001**	**1856 (901.4-3821) *P*<0.0001**	**9107 (5260-15767) *P*<0.0001**	3451 (875.8-13598) *P*=0.100	**2642 (696.6-10024) *P*=0.0152**	1023 (55.1-18978) *P*=0.1143	—	**1383 (942.8-2028) *P* <0.0001**	**4112 (2333-7248) *P* <0.0001**	**2831 (1922-4169) *P* <0.0001**
GII.4_SF												
Pre-Vx	32.3 (27.6-37.9)	96.7 (51.9-180.2)	107.8 (75.2-154.4)	153.0 (74.9-312.7)	208.8 (127.0-343.3)	139.4 (16.7-1167)	120.9 (30.2-483.5)	30.0 (30.0-30.0)	—	115.4 (86.62-153.8)	125.3 (79.48-197.6)	39.8 (34.3-46.3)
Post-Vx	32.8 (27.1-39.8) *P* >0.9999	124.2 (63.6-242.3) *P*=0.5864	**382.3 (231.0-632.7) *P*<0.0001**	396.1 (191.9-817.4) **P=0.0803**	**1190.0 (741.2-1910) *P*=0.0001**	1204 (115.0-12597) *P*=0.100	397.1 (98.1-1607) *P*=0.1277	121.3 (8.9-1644) *P*=0.4286	—	**301.4 (211.3-430.0) *P*<0.0001**	**618.9 (351.0-1091) *P* <0.0001**	**129.2 (100.0-166.9) *P* <0.0001**
GII.4_SY												
Pre-Vx	41.9 (20.6-85.4)	637.2 (199.5-2035)	644.9 (349.9-1188)	792.1 (341.0-1840)	1668 (1040-2676)	1118 (934.9-1336)	618.1 (117.3-3256)	173.1 (6.8-4382)	—	679.0 (435.6-1058)	848.7 (467.6-1540)	87.3 (65.5-111.1)
Post-Vx	44.1 (21.8-89.4) *P* >0.9999	795.3 (211.4-2993) *P*=0.3553	**2763 (1204-6343) *P*=0.0001**	**2802 (970.3-8092) *P*=0.0076**	**16079.0 (10855-23818) *P*<0.0001**	7391 (2206-24771) *P*=0.100	**3527.0 (421.5-29509) *P*=0.0411**	442.7 (3.1-64142) *P*=0.6571	—	**2109 (1185-3755) *P*<0.0001**	**5487 (2345-12839) *P* <0.0001**	**491.7 (344.5-701.8) *P* <0.0001**
GII.4_WI												
Pre-Vx	40.8 (24.9-66.7)	234.7 (101.6-542.3)	207.2 (132.7-323.7)	289.3 (137.3-609.8)	529.8 (341.8-808.8)	548.6 (252.5-1192)	383.3 (86.8-1692)	141.3 (7.5-2661)	—	232.6 (165.5-326.9)	392.4 (242.3-635.4)	54.2 (44.4-66.2)
Post-Vx	40.4 (25.5-64.1) *P* >0.9999	267.6 (114.7-624.2) *P*=0.9452	**625.8 (351.6-1114) *P*=0.0013**	630.3 (294.8-1348) **P=0.1397**	**3448 (2298-5173) *P*<0.0001**	3253 (523.4-20212) *P*=0.100	**1287 (180.5-9172) *P*=0.0433**	307.4 (4.0-23420) *P*=0.6571	—	**520.2 (350.1-773.0) *P*=0.0007**	**1788 (887.2-3604) *P* <0.0001**	**259.5 (191.2-352.2) *P* <0.0001**
GII.4_AL												
Pre-Vx	34.3 (25.8-45.7)	169.7 (83.6-344.3)	136.9 (92.4-202.7)	165.4 (86.7-315.3)	344.8 (212.3-559.8)	248.7 (16.3-3803)	174.1 (63.1-480.7)	72.5 (9.7-541.6)	—	150.8 (112.3-202.5)	215.2 (139.0-333.0)	56.0 (45.4-69.1)
Post-Vx	34.6 (25.5-47.0) *P* >0.9999	239.3 (100.3-570.9) *P*=0.4248	**938.3 (491.9-1790) *P*<0.0001**	**844.5 (352.1-2025) *P*=0.0029**	**4673 (2870-7608) *P*<0.0001**	2084 (485.4-8946) *P*=0.100	**1124 (164.1-7700) *P*=0.0433**	259.1 (4.1-16374) *P*=0.6571	—	**675.9 (432.2-1057) *P*<0.0001**	**1827 (876.6-3807) *P* <0.0001**	**367.9 (271.3-498.9) *P* <0.0001**
GII.4_US95/96												
Pre-Vx	33.3 (26.7-41.5)	81.2 (44.6-148.0)	81.9 (57.1-117.7)	111.4 (57.9-214.4)	131.6 (63.6-272.7)	41.8 (10.1-173.5)	70.8 (30.8-162.8)	60.8 (16.4-225.4)	—	88.69 (67.30-116.9)	85.88 (56.90-129.6)	283.0 (192.2-416.8)
Post-Vx	34.0 (26.1-44.3) *P*>0.9999	113.9 (62.4-207.7) *P*=0.3342	**278.2 (176.8-437.7) *P*=0.0001**	304.4 (147.8-626.8) **P=0.0527**	**1758 (1121-2759) *P*<0.0001**	891.2 (29.1-27327) *P*=0.100	**604.9 (215.1-1702) *P*=0.0043**	222.2 (5.2-9456) *P*=0.6571	—	**234.1 (168.8-324.6) *P*<0.0001**	**876.3 (490.3-1566) *P* <0.0001**	**1942 (1171-3220) *P* <0.0001**

Table S18. GII.4 sNAb GMFR (95% CI) in infants, toddlers, and children aged 0.5-<9 years in the NOR-202 study and adults aged 18-<50 years in the NOR-215 study. Sera were collected pre-vaccination (Pre-Vx) and 28 days post-dose 1 vaccination (Post-Vx) with HIL-214 (for NOR-202 combined formulations/compositions groups, see **Table S15**). GMFR ≥4.0 are bolded.

Age Group	Number of participants, N											
	NOR-202											NOR-215
	HIL-214 (1 dose of 15/50, 50/50, or 50/150 µg; combined)											1x 50/150 µg
	0.5-<1 yr (N=16)	1-<2 yr (N=20)	2-<3 yr (N=47)	3-<4 yr (N=24)	4-<5 yr (N=11)	5-<6 yr (N=3)	6-<7 yr (N=6)	7-<8 yr (N=4)	8-<9 yr (N=0)	1-<4 yr (N=91)	4-<9yr (N=24)	18-<50 yr (N=77)
GII.4 sNAb, GMFR (95% CI)												
GII.4c	2.8 (1.7-4.6)	3.5 (1.9-6.4)	**14.2 (9.5-21.3)**	**11.7 (5.3-25.5)**	**19.0 (9.7-37.2)**	**29.5 (2.6-338.6)**	**15.6 (7.5-32.3)**	**12.6 (2.5-64.1)**	—	**9.9 (7.2-13.8)**	**17.8 (12.2-26.1)**	**16.5 (12.4-21.9)**
GII.4_SF	1.0 (1.0-1.1)	1.3 (0.8-2.1)	3.5 (2.4-5.2)	2.6 (1.3-5.1)	**5.7 (2.8-11.6)**	**8.6 (6.6-11.4)**	3.3 (1.2-9.2)	**4.0 (0.3-54.8)**	—	2.6 (2.0-3.5)	**4.9 (3.1-7.8)**	3.2 (2.6-4.1)
GII.4_SY	1.1 (0.9-1.2)	1.2 (0.7-2.1)	**4.3 (2.9-6.3)**	3.5 (2.1-6.0)	**9.6 (5.9-15.8)**	**6.6 (2.6-18.6)**	**5.7 (2.5-12.9)**	2.6 (0.4-14.7)	—	3.1 (2.3-4.1)	**6.5 (4.5-9.4)**	**5.6 (4.3-7.4)**
GII.4_WI	1.0 (0.9-1.1)	1.1 (0.8-1.7)	3.0 (2.1-4.3)	2.2 (1.3-3.6)	**6.6 (3.6-11.8)**	**5.9 (1.1-33.1)**	3.4 (1.5-7.7)	2.2 (0.5-9.1)	—	2.2 (1.7-2.9)	**4.6 (3.1-6.7)**	**4.8 (3.7-6.2)**
GII.4_AL	1.0 (1.0-1.0)	1.4 (0.8-2.6)	**6.9 (4.3-11.0)**	**5.1 (2.4-10.9)**	**13.6 (7.1-25.6)**	**8.4 (1.7-41.7)**	**6.5 (1.9-22.0)**	3.6 (0.3-37.2)	—	**4.5 (3.1-6.4)**	**8.5 (5.3-13.6)**	**6.6 (5.0-8.7)**
GII.4_US95/96	1.0 (1.0-1.1)	1.4 (0.8-2.3)	3.4 (2.3-4.9)	2.7 (1.4-5.3)	**13.4 (5.2-34.2)**	**21.3 (0.4-1216)**	**8.5 (4.4-16.4)**	3.7 (0.3-46.8)	—	2.6 (2.0-3.5)	**10.2 (5.8-18.0)**	**6.9 (5.3-9.0)**

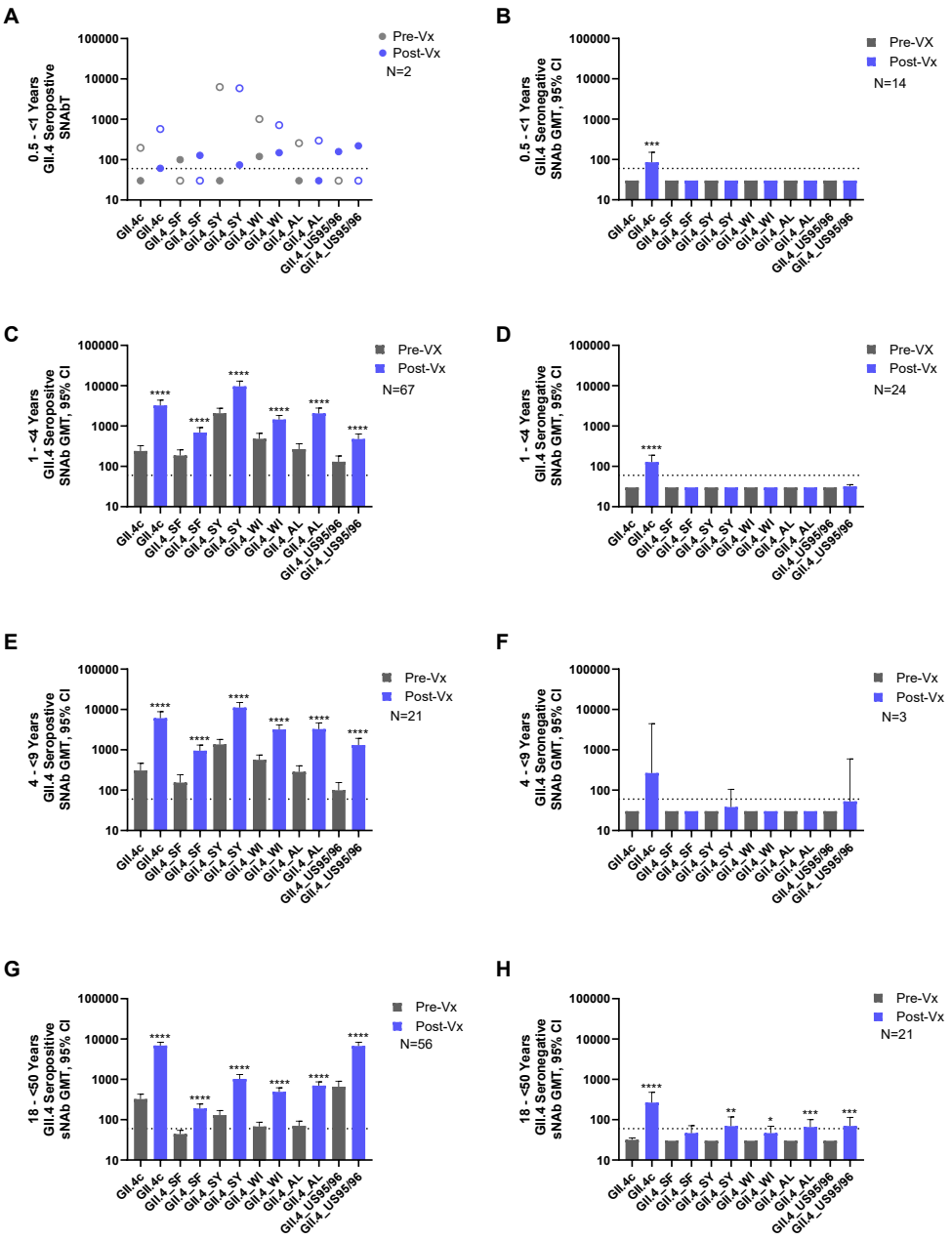
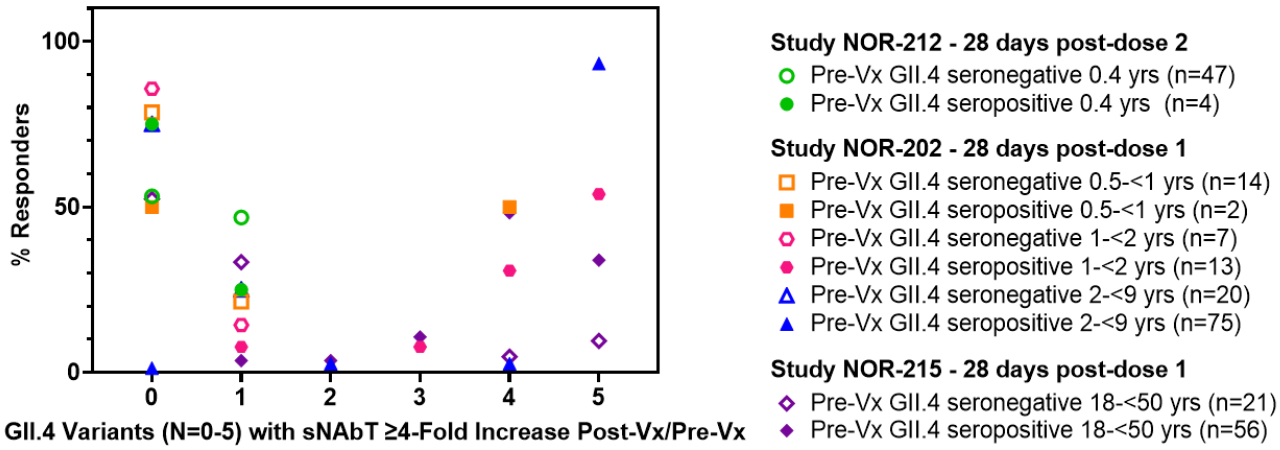


Figure S4 GII.4 sNAb responses by pre-vaccination serostatus following HIL-214 vaccination in participants aged 0.5-<50 years in the NOR-202 and NOR-215 studies. Archived sera collected from infants (N=16; aged 0.5-<1 yrs), toddlers (N=91; aged 1-<4 yrs), children (N=22; aged 4-<9 yrs) (NOR-202 study; combined compositions (15/50, 50/50, 50/150 μg); conducted from 2015-2018) and adults (N=77; aged 18-<50 yrs) (NOR-215 study; 50/150 μg composition; conducted in 2023) at Day 1/pre-vaccination (Pre-Vx) and 28 days post-vaccination (Post-Vx) with a single dose of HIL-214, were analyzed for sNAbT breadth against GII.4c, contemporary variants (GII.4_SF, GII.4_SY, GII.4_WI, GII.4_AL) and an ancestral variant (GII.4_US96/96). **(A)** infants, **(B)** toddlers, (**C**) children, and **(D)** adults were grouped by Pre-Vx GII.4 variant seropositivity (ID50 ≥60 to any variant) (**Panels A, C, E**) or GII.4 seronegativity (**Panels B, D, F**) and GII.4 sNAbT measured at 28 days Post-Vx. *, *P*<0.05; **, *P*<0.01; *** *P*<0.001; **** *P*<0.0001, Mann-Whitney test comparing Pre-Vx to Post-Vx. Two infants (closed and hollow circles) were GII.4 seropositive Pre-Vx and their GII.4 sNAbTs are shown as individual points in panel A at Pre-Vx and Post-Vx.

A



B

GII.4 Variant Breadth rate Differences by Pre-Vx GII.4 Serostatus

			P Values				
Seronegative	Study	Age at Vx (yrs)	0.4	0.5-<1	1-<2	2-<9	18-<50
	NOR-212	0.4	-	-	-	-	-
	NOR-202	0.5-<1	0.3006	-	-	-	-
	NOR-202	1-<2	0.3188	0.8480	-	-	-
	NOR-202	2-<9	0.3188	0.8987	0.7619	-	-
	NOR-215	18-<50	0.0118	0.0118	0.0147	0.0029	-
Seropositive	Study	Age at Vx (yrs)	0.4	0.5-<1	1-<2	2-<9	18-<50
	NOR-212	0.4	-	-	-	-	-
	NOR-202	0.5-<1	0.0231	-	-	-	-
	NOR-202	1-<2	<0.0001	0.0010	-	-	-
	NOR-202	2-<9	<0.0001	<0.0001	0.0257	-	-
	NOR-215	18-<50	<0.0001	0.0013	0.5175	<0.0001	-

Figure S5. GII.4 sNAb response breadth and magnitude by ICH E11 age strata and pre-vaccination GII.4 serostatus (NOR-212, NOR-202, NOR-215). Infants (N=26 HIL-214 (GII.4 AGE+ group) + N=25 HIL-214 (GI/GII AGE- group) combined; aged 0.4 yrs) from NOR-212 (2-doses: 50/150 μg composition; **Table S11**), infants (N=16 HIL-214; aged 0.5-1 yr), toddlers (N=91 HIL-214; aged 1-<4 yrs), children (N=22 HIL-214; aged 4-<9 yrs) from NOR-202 (1-dose: combined compositions (15/50, 50/50, 50/150 μg); **Table S15**), and adults (N=77 HIL-214; aged 18<50 yrs; **Table S16**) from NOR-215 (1-dose: 50/150 μg composition) were grouped by age according to ICH E11 guidelines (0.5-<1 yr, 1-<2 yrs, 2-<9 years, 18-<50 yrs) and GII.4 serostatus Day 1/pre-vaccination (Pre-Vx). **(A)** %Responders (GII.4 sNAbT breadth rate) shown as the proportion of participants in each age group with a ≥4-fold increase in GII.4 sNAbT at 28 days post-vaccination (Post-Vx) compared to pre-vaccination values against 0 to 5 GII.4 variants. **(B)** Linear regression models were fitted to estimate the association between age and pre-vaccination GII.4 serostatus to post-vaccination GII.4 sNAbT with *P* values (Cochran-Mantel-Haenszel) of each comparison reported. **Table S14** shows the number of respondents with a ≥4-fold increase in sNAbT to GII.4 variants by variant number (N=0-5), study, and age grouping at HIL-214 vaccination.

Citations:

1. Freedman, S.B., Eltorky, M. & Gorelick, M. Evaluation of a gastroenteritis severity score for use in outpatient settings. *Pediatrics* **125**, e1278-1285 (2010).
2. Vesikari, T.*, et al*. Immunogenicity of a bivalent virus-like particle norovirus vaccine in children from 1 to 8 years of age: A phase 2 randomized, double-blind study. *Vaccine* **40**, 3588-3596 (2022).
3. Lopez, P.*, et al*. Immunogenicity and tolerability of a bivalent virus-like particle norovirus vaccine candidate in children from 6 months up to 4 years of age: A phase 2 randomized, double-blind trial. *Hum Vaccin Immunother* **19**, 2204787 (2023).
4. Sáez-Llorens, X.*, et al*. Safety and immunogenicity of a bivalent norovirus vaccine candidate in infants from 6 weeks to 5 months of age: A phase 2, randomized, double-blind trial. *Human vaccines & immunotherapeutics* **21**, 2450878 (2025).
5. Hillevax, I. NOR-215: Phase 2, Single-arm, Open-label Trial for Serologic Assay Validation, Proficiency Testing, Safety and Immunogenicity of the Intramuscular HIL-214 Norovirus Vaccine in Adults Aged 18 to 49 Years. Vol. 2025 NCT05972733 (CT.gov, 2025).