RotaTeq™ (Rotavirus Vaccine, Live, Oral, Pentavalent)

Update for the 12th International Rotavirus Symposium

Susan S. Kaplan, MD, MHS

Merck & Co., Inc., Kenilworth, NJ, USA

Presentation Outline

- Updates on RotaTeq™ (RV5)
- Review of Key Clinical Data Presentations at the International Rotavirus Symposium
  - Safety and Immunogenicity of Pentavalent Rotavirus Vaccine in HIV-Infected and HIV-Exposed Infants in Africa (IMPAACT P1072)
  - Efficacy and Safety of a Pentavalent Live Human-Bovine Reassortant Rotavirus Vaccine (RV5) in Healthy Chinese Infants: A Randomized, Double-Blind, Placebo-Controlled Trial
  - Safety, Tolerability, and Immunogenicity of Pentavalent Rotavirus Vaccine Manufactured by a Modified Process
- Summary of presentations at the International Rotavirus Symposium related to RV5

RV5: Key Facts

- Live, oral, pentavalent vaccine for the prevention of rotavirus gastroenteritis in infants and children caused by G1, G2, G3, G4, and G- serotypes that contain P1A[8] (e.g. G9)
- Licensed in >120 countries since 2006
- >179 million doses distributed worldwide (as of 2Q2016)
- Efficacy in high and low-income countries
  - Effective against varying strains and through 7 years of life
- Safety profile demonstrated in large, comprehensive pre- and post-licensure studies and global post-licensure surveillance for 10 years
- Public health benefits within a few years of introduction, including:
    - Delayed and diminished rotavirus seasonal activity
    - Evidence of herd protection
    - Reduction in healthcare utilization
    - Improved timeliness and compliance of other 3 dose pediatric vaccines

Safety and Immunogenicity of RV5 in HIV-Infected and HIV-Exposed Infants in Africa (IMPAACT P1072)

- Randomized, multicenter, double-blind, clinical study
  - In collaboration with IMPAACT (The International Maternal Pediatric Adolescent AIDS Clinical Trials Network)
  - 5 IMPAACT sites in 4 African countries (Botswana, Tanzania, Zambia, Zimbabwe)
  - evaluate the safety and immunogenicity of RV5 in HIV+ and HIV exposed-uninfected (HEU) infants born to HIV+ mothers
    - Immunogenicity was assessed by serum neutralizing antibodies (G1-G4, P1A) and anti-RV IgA
- 202 infants (76 HIV+, 126 HEU) randomized
  - Median CD4% for HIV+: 29% (range 7-58)

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Study Design: RV5 in HIV+/HEU in Africa

	Days Post-Dose												
	Dose 1				Dose 2				Dose 3				
	0	7	14	21	42/0	7	14	21	42/0	7	14	21	42
Vaccine	X				X				X				
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood	X										X		X§
Stool*	X	X	X	X		X		X		X		X	

§ if not collected at 14 days PD3

* plus any unplanned visits for gastroenteritis

RV5 Safety in HIV+ in Africa

(entire study; combines all visits)

CD4	Events	RV5 (n=5)	Placebo (n=6)
<20% (n = 11)	≥grade 3 *	0 (0%)	1 (17%)
	≥grade 2 *	0 (0 %)	1 (17%)
	Diarrhea	0 (0 %)	0 (0%)
	Vomiting	1 (20%)	2 (33%)
		(n=32)	(n=33)
≥20% (n = 65)	≥grade 3 *	1 (3%)	0 (0%)
	≥grade 2 *	2 (6%)	1 (3%)
	Diarrhea	14 (44%)	10 (30%)
	Vomiting	9 (28%)	4 (12%)

- 3 Deaths – 1 RV5; 2 placebo; none related to RV5
- 8 Hospitalizations – 5 RV5; 3 placebo (0 related)
- No significant differences in growth
- No HIV diagnosis in HEU
- No cases of intussusception

*possibly/probably/definitely vaccine related

Immunogenicity: RV5 in HIV+/HEU in Africa
Seroresponse rates 14 days Postdose 3

RV Antibody	Cohort	Placebo Response/N	RV5 Response/N†‡
SNA G1 (dilution/mL)	HIV+	1/32 (3%)	18/34 (53%)
	HEU	1/58 (2%)	18/57 (32%)
SNA G2 (dilution/mL)	HIV+	3/32 (9%)	8/34 (24%)
	HEU	3/58 (5%)	7/57 (12%)
SNA G3 (dilution/mL)	HIV+	0/32 (0%)	10/34 (29%)
	HEU	1/58 (2%)	12/57 (21%)
SNA G4 (dilution/mL)	HIV+	1/32 (3%)	21/34 (62%)
	HEU	3/58 (5%)	18/57 (32%)
SNA P1 (dilution/mL)	HIV+	4/32 (13%)	8/33 (24%)
	HEU	5/58 (9%)	14/56 (25%)
IgA (units/mL)	HIV+	5/31 (16%)	26/32 (81%)
	HEU	17/58 (29%)	46/57 (81%)

†Differences between RV5 and placebo were significant for each antibody tested except G2 and P1. Differences between HIV+ and HEU were not significant.

RV5 in HIV+/HEU in Africa: Conclusions

- RV5 was safe and well tolerated in both HIV+ and HEU infants
- Statistically significantly higher immune responses were seen in recipients of RV5 compared to placebo in both HIV strata, and Postdose 3 antibody levels did not differ by HIV status
- Shedding of RV5 in stool was similar to that previously reported in uninfected infants and was not prolonged in HIV+ vaccinees

Efficacy and Safety of RV5 in Healthy Chinese Infants

- China has experienced significant morbidity and economic burden associated with rotavirus infection.
- Randomized, multicenter, double-blind, placebo-controlled clinical study to evaluate the safety and efficacy of RV5 in healthy Chinese infants
  - 3 doses of RV5 or placebo administered starting at 6 weeks of age; EPI vaccines (OPV and DTaP) administered on a concomitant or staggered schedule
  - Efficacy assessed through 2014-15 rotavirus season
  - Subjects were followed for safety for 30 days after each dose; SAEs, deaths, and cases of intussusception were collected for the duration of the study
- 4040 infants randomized

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Adverse Event Summary RV5 in Chinese Infants: 30 Days Following any Vaccination in All Subjects as Treated Population

	RV5		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population with follow-up	2,015		2,019		4,034	
with one or more AE	1,079	(53.5)	1,077	(53.3)	2,156	(53.4)
with no AE	936	(46.5)	942	(46.7)	1,878	(46.6)
with vaccination-related† AE	359	(17.8)	354	(17.5)	713	(17.7)
with serious AE	116	(5.8)	116	(5.7)	232	(5.8)
with serious vaccination-related AE	0	(0.0)	3	(0.1)	3	(0.1)
who died	0	(0.0)	0	(0.0)	0	(0.0)
discontinued‡ due to an AE	17	(0.8)	12	(0.6)	29	(0.7)
discontinued due to a vaccination-related AE	4	(0.2)	4	(0.2)	8	(0.2)
discontinued due to a serious AE	10	(0.5)	5	(0.2)	15	(0.4)
discontinued due to a serious vaccination-related AE	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the vaccination.

‡ Study medication withdrawn.

All events were collected within 30 days after any vaccination and before next vaccination.

2 cases of intussusception in the RV5 group; occurred >30 days Postdose 1 and Postdose 3, respectively

Vaccine Efficacy of RV5 in Chinese Infants at Least 14 Days Postdose 3 in the Per-Protocol Population

	RV5 (N=2018)	Placebo (N=2019)	Efficacy % (95% CI)
RVGE any-severity regardless of serotype	34	109	69.3 (54.5, 79.7)
RVGE severe regardless of serotype	11	52	78.9 (59,1, 90.1)

N= number vaccinated
Vesikari scoring system was used to determine RVGE severity. A severity score ≥11 was considered as severe

Conclusions: RV5 in Chinese Infants

- In healthy Chinese infants, RV5 was
  - efficacious against naturally-occurring any-severity and severe RVGE regardless of serotype at least 14 days following the third vaccination.
  - generally well-tolerated with respect to all AEs and when concomitantly administered with OPV and DTaP.

Safety, Tolerability, and Immunogenicity of RV5 Manufactured by a Modified Process

- A modified formulation of RV5 has been developed ($RV5_{mp}$)
  - stability at 37°C for 7 days
  - expiry extended to 36 months when stored at 2 to 8°C
- Randomized, multicenter, double-blind, clinical study to demonstrate noninferiority of $RV5_{mp}$ to the current formulation of RV5 on the basis of safety and immunogenicity
  - 3 doses of RV5 or $RV5_{mp}$ administered beginning at 6 weeks of age, approved routine pediatric vaccines administered on same day
  - Immunogenicity assessed at baseline and 42 days Postdose 3 by serum neutralizing antibodies (G1-G4, P1A) and anti-RV IgA
  - Subjects were followed for safety for 42 days after each dose; SAEs, deaths, and cases of intussusception were collected for the duration of the study
- 1020 healthy infants randomized

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Immunogenicity of $RV5_{mp}$: Statistical Analysis of Non-inferiority of GMT for the SNA Responses (Per Protocol Population)

Antigen	$RV5_{mp}$ (N=495)		RV5 (N=488)		GMT Ratio†‡	95% CI §	P-value
	n	Estimated GMT†	n	Estimated GMT†			
Serotype G1	495	99.5	488	107.6	0.92	(0.79, 1.07)	<0.001
Serotype G2	495	30.7	488	26.7	1.15	(0.99, 1.33)	<0.001
Serotype G3	495	82.6	488	25.8	3.20	(2.75, 3.74)	<0.001
Serotype G4	495	77.3	488	72.8	1.06	(0.94, 1.20)	<0.001
Serotype P1A	495	107.2	488	92.5	1.16	(1.00, 1.35)	<0.001

† GMTs and their ratio were based on a model with terms for treatment and country, with the constraint that the mean baseline is the same for all treatment groups.

‡ $RV5_{mp}$ / RV5.

§ A 95% CI on the ratio excluding a 1.5fold decrease or more (i.e., the lower bound of CI > 0.67) and associated 1-sided p-value ≤ 0.025 implies that the difference is statistically significantly less than the pre-specified clinically relevant decrease of 1.5-fold and allows for a conclusion of non-inferiority.

SNA = Serum neutralization assay.

N = Number of subjects vaccinated.

n = Number of subjects contributing to the per-protocol analyses.

CI = Confidence interval.

Safety of $RV5_{mp}$: Adverse Experience Summary Following Any Vaccination

Parameter	$RV5_{mp}$ (N=509)		RV5 (N=505)	
	n	(%)	n	(%)
With one or more AE	439	(86.4)	438	(87.8)
Diarrhea (Day 1 to 7)	144	(28.3)	128	(25.7)
Vomiting (Day 1 to 7)	84	(16.5)	92	(18.4)
Temperature ≥38.1° C (Day 1 to 7)	217	(42.7)	223	(44.7)
Irritability (Day 1 to 7)	58	(11.4)	64	(12.8)
With vaccine-related* AEs (Day 1 to 42)	259	(51.0)	256	(51.3)
Diarrhea (Day 1 to 7)	124	(24.4)	104	(20.8)
Vomiting (Day 1 to 7)	65	(12.8)	68	(13.6)
Temperature ≥38.1° C (Day 1 to 7)	84	(16.5)	79	(15.8)
Irritability (Day 1 to 7)	44	(8.7)	49	(9.8)
With serious AEs (any time postvaccination)	20	(3.9)	12	(2.4)
Vaccine-related* serious AEs	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)
Discontinued due to AE	2†	(0.4)	0	(0.0)

* = Determine by the investigator to be possibly, probably, or definitely related to the vaccine

† = (1) intussusception, 45 days postdose 2, severe intensity, investigator-assessed as not related to study vaccine; (2) intussusception, 37 days postdose 2, severe intensity, investigator-assessed as not related to study vaccine

N = Number of subjects in population with follow-up

n = Number of subjects in each category

The same subject may appear in different categories, but counted only once in each category

Conclusions: safety and immunogenicity of $RV5_{mp}$

- $RV5_{mp}$ was non-inferior to the current formulation of RV5 with respect to immunogenicity.

- $RV5_{mp}$ was well-tolerated and had a similar safety profile as the current formulation of RV5.

Presentations at International Rotavirus Symposium Pertaining to RV5

- Clinical Data
  - Safety and Immunogenicity of Pentavalent Rotavirus Vaccine in HIV-Infected and HIV-Exposed Infants in Africa (IMPAACT P1072) [Poster #27]
  - Efficacy and Safety of a Pentavalent Live Human-Bovine Reassortant Rotavirus Vaccine (RV5) in Healthy Chinese Infants: a Randomized, Double-Blind, Placebo-Controlled Trial [Poster #42]
  - Safety, Tolerability, and Immunogenicity of Pentavalent Rotavirus Vaccine Manufactured by a Modified Process [Poster #26]
- Outcomes Research
  - Vaccine Coverage at Milestone Ages Among Infants in the United States [Poster #111]
- Hilleman Labs
  - Evaluation of safety and immunogenicity of an oral, lyophilized, lie attenuated, pentavalent (G1, G2, G3, G4 AND P1A[8]), heat-stable rotavirus vaccine (HSRV5) in healthy adults and infants in Bangladesh [oral presentation, Session X]