

Clinical Support for the Efficacy of Rotarix - Potency

Date: March 14, 2008

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Subject: Clinical support for the efficacy of Rotarix (STN 125265/0) at a potency of less than $10^{6.5}$ CCID₅₀ per dose against rotavirus gastroenteritis

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During internal CBER discussions involving the release potency of Rotarix, concerns were raised over the requirement that the sponsor release vaccine lots at $10^{6.5}$ CCID₅₀ per dose. By factoring in the variability of the potency assay and the stability of the product, a lot released at $10^{6.5}$ CCID₅₀ could potentially have a potency as low as $10^{6.1}$ CCID₅₀. The efficacy of vaccine doses below $10^{6.5}$ CCID₅₀ was not evaluated in the large randomized controlled pivotal efficacy trials Rota-023 and Rota-036. However, the available clinical efficacy and immunogenicity data from Phase 2 clinical trials in the BLA provide evidence that a potency as low as $10^{6.1}$ CCID₅₀ would likely be protective among infants in the United States (Tables 1 and 2).

Clinical Efficacy

Study Rota-004, conducted in Finland, demonstrated a vaccine efficacy of 90.0% (95% CI: 10.3, 99.8) against severe RV GE at a potency of $10^{5.3}$ CCID₅₀ per dose (Table 1).

Although the 95% CI was wide due to the relatively small sample size (N=368), this estimate was higher than the point estimates for the corresponding $10^{5.3}$ CCID₅₀ group (65.8%; 95% CI: 32.2, 83.9) and the $10^{6.6}$ CCID₅₀ group (85.6%; 95% CI: 63.0, 95.6) in Rota-006, conducted in Latin America. The efficacy point estimate in Rota-004 was also higher than in Rota-023 (84.8%; 95% CI: 71.1, 92.7) (Latin America) and similar to Rota-036 (95.8%; 95% CI: 89.6, 98.7) (Europe).

In Rota-004, the efficacy point estimate against RV GE of any severity at a potency of $10^{5.3}$ CCID₅₀ was also higher than both the $10^{5.3}$ CCID₅₀ and $10^{6.6}$ CCID₅₀ groups in Rota-006 (Table 1).

Although the efficacy estimates from Rota-004 have wide 95% CIs due to the relatively small sample size, these data provide evidence that at a potency well below $10^{6.5}$ CCID₅₀, Rotarix protects against RV GE; additionally, efficacy is consistently higher in a developed country compared to a developing country. Similarly, higher efficacy against severe RV GE was observed in the European pivotal trial (Rota-036) compared to the Latin America pivotal trial (Rota-023) (Table 1). This is consistent with what is observed with other enteric vaccines, such as OPV, which have higher efficacy in developed countries compared with developing countries.

While clinical trials at potencies of $10^{6.1}$ CCID₅₀ have not been conducted in Finland or elsewhere in Europe, it is likely that efficacy against RV GE would be higher than estimates obtained at potency of $10^{5.3}$ CCID₅₀ in Rota-004. Due to socioeconomic and demographic similarities between Europe and the US, the degree of efficacy would very likely be similar in both geographic regions.

Immune Response

Presently, there is no immune correlate of protection for RV GE. However, anti-RV IgA has generally been considered the standard measure of immunity in most field studies and vaccine trials. In Rota-006, the anti-RV IgA GMC was higher in the $10^{6.6}$ CCID₅₀ group compared to the $10^{5.6}$ CCID₅₀ group (Table 2). In Rota-005 (US, Canada), the anti-RV IgA GMC was also higher in the $10^{6.6}$ CCID₅₀ group compared to the $10^{5.6}$ CCID₅₀ group.

However, the point estimate for the $10^{5.6}$ CCID₅₀ group in Rota-005 was higher than the $10^{6.6}$ CCID₅₀ group in Rota-006 (Table 2). In Rota-007 (Singapore), the point estimate for the $10^{5.6}$ CCID₅₀ group was not only higher than the $10^{6.6}$ CCID₅₀ group in Rota-006, but was also higher than the $10^{6.6}$ CCID₅₀ group in the same study (Rota-007).

These immunogenicity comparisons between studies parallel efficacy comparisons described above. The lower potency groups in Rota-005 and Rota-007, conducted in developed countries, demonstrated better anti-RV IgA immunogenicity than the higher potency group in Rota-006, conducted in less developed countries in Latin America. In Rota-007, the GMC point estimate for the lower potency group was even higher than the high potency group. Although immunogenicity at potencies of $10^{6.1}$ CCID₅₀ or $10^{6.2}$ CCID₅₀ were not evaluated in the US/Canada or Singapore, it is likely that anti-RV IgA GMC would be both higher than estimates obtained at $10^{5.6}$ CCID₅₀ and similar to estimates obtained at $10^{6.5}$ CCID₅₀ during the trials.

Conclusion

Based on adequate and well controlled clinical trials of Rotarix at a potency of $10^{6.5}$ CCID₅₀ (Rota-023 and Rota-036) and supplementary data from Phase 2 trials (Rota-004 and Rota-006) the clinical reviewers are confident to conclude that a Rotarix lot potency of $10^{6.1}$ CCID₅₀ would provide significant and meaningful protection against RV GE in the U.S.

Table 1: ATP efficacy summary (% , 95% CI)

Year 1						
Endpoint	Rota-023	Rota-036	Rota-004	Rota-006 (2-dose subset)		
RV GE	$10^{6.5}$ CCID ₅₀	$10^{6.5}$ CCID ₅₀	$10^{5.3}$ CCID ₅₀	$10^{5.3}$ CCID ₅₀	$10^{5.6}$ CCID ₅₀	$10^{6.6}$ CCID ₅₀
Any		87.1 (79.6, 92.1)	73.0 (27.1, 90.9)	58.4 (29.4, 76.3)	55.7 (25.3, 74.5)	70.0 (45.7, 84.4)
Severe	84.8 (71.1, 92.7)	95.8 (89.6, 98.7)	90.0 (10.3, 99.8)	65.8 (32.2, 83.9)	71.0 (39.9, 87.2)	85.6 (63.0, 95.6)

Table 2: ATP immunogenicity summary

Seroconversion rate– % (95% CI)						
Endpoint	Rota-006 (Latin America)		Rota-005 (US, Canada)		Rota-007 (Singapore)	
	$10^{5.6}$ CCID ₅₀	$10^{6.6}$ CCID ₅₀	$10^{5.6}$ CCID ₅₀	$10^{6.8}$ CCID ₅₀	$10^{5.6}$ CCID ₅₀	$10^{6.6}$ CCID ₅₀
2 months post-Dose 2	62.4 (53.3, 70.9)	65.3 (56.3, 73.6)	67.4 (58.9, 75.1)	78.2 (70.2-84.9)	87.3 (80.9, 92.2)	85.0 (78.5-90.1)

GMC – U/mL (95% CI)

Endpoint	Rota-006 (Latin America)		Rota-005 (US, Canada)		Rota-007 (Singapore)	
	$10^{5.6}$ CCID ₅₀	$10^{6.6}$ CCID ₅₀	$10^{5.6}$ CCID ₅₀	$10^{6.8}$ CCID ₅₀	$10^{5.6}$ CCID ₅₀	$10^{6.6}$ CCID ₅₀
2 months post-Dose 2	52.1 (39.7, 68.3)	70.7 (51.9, 96.3)	80.1 (59.5, 107.0)	117.0 (88.3-154.9)	139.6 (112.0, 174.0)	112.1 (89.0-141.1)