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Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian children in the second year of life



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ABSTRACT

Rotavirus gastroenteritis is one of the leading causes of diarrhea in Indian children less than 2 years of age. The 116E rotavirus strain was developed as part of the Indo-US Vaccine Action Program and has undergone efficacy trials. This paper reports the efficacy and additional safety data in children up to 2 years of age.

In a double-blind placebo controlled multicenter trial, 6799 infants aged 6–7 weeks were randomized to receive three doses of an oral human-bovine natural reassortant vaccine (116E) or placebo at ages 6, 10, and 14 weeks. The primary outcome was severe (≥ 11 on the Vesikari scale) rotavirus gastroenteritis. Efficacy outcomes and adverse events were ascertained through active surveillance. We randomly assigned 4532 and 2267 subjects to receive vaccine and placebo, respectively, with over 96% subjects receiving all three doses of the vaccine or placebo. The per protocol analyses included 4354 subjects in the vaccine and 2187 subjects in the placebo group. The overall incidence of severe RVGE per 100 person years was 1.3 in the vaccine group and 2.9 in the placebo recipients. Vaccine efficacy against severe rotavirus gastroenteritis in children up to 2 years of age was 55.1% (95% CI 39.9 to 66.4; $p < 0.0001$); vaccine efficacy in the second year of life of 48.9% (95% CI 17.4 to 68.4; $p = 0.0056$) was only marginally less than in the first year of life [56.3% (95% CI 36.7 to 69.9; $p < 0.0001$)]. The number of infants needed to be immunized to prevent one episode of severe RVGE in the first 2 years of life was 40 (95% CI 28.0 to 63.0) and for RVGE of any severity, it was 21 (95% CI 16.0 to 32.0). Serious adverse events were observed at the same rates in

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² See Appendix A.

the two groups. None of the eight intussusception events occurred within 30 days of a vaccine dose and all were reported only after the third dose.

The sustained efficacy of the 116E in the second year of life is reassuring.

Clinical Trial Registry: The trial is registered with Clinical Trial Registry-India (# CTRI/2010/091/000102) and Clinicaltrials.gov (# NCT01305109).

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1. Introduction

Rotavirus continues to be one of the leading causes of diarrhea in children under 5 years of age and is a particular problem in India, which harbors almost one-fourth of the estimated number of rotavirus deaths in the world [1]. Most cases of rotavirus gastroenteritis (RVGE) occur in children below 2 years of age [2]. In developing countries, most of the burden of rotavirus disease occurs in the first year of life but there remains a substantial burden in the second year of life as well [3,4]. As reported by the Indian Rotavirus Surveillance Network, 36.5% and 38.9% of hospitalized cases were rotavirus associated, in infants aged 6–11 months and children aged 12–23 months respectively [5].

The 116E rotavirus vaccine was developed from a neonatal human rotavirus strain identified in India, as part of the Indo-US Vaccine Action Program [6]. The 116E rotavirus strain, G9P[11], is a naturally occurring reassortant containing one bovine rotavirus gene P[11] and ten human rotavirus genes [7,8]. The 116E vero cell based rotavirus vaccine was assessed for efficacy against severe rotavirus gastroenteritis in a multi-center, randomized placebo controlled trial in India and safety and efficacy during the first year of follow up have recently been published [9].

We now report the efficacy and additional safety data for the second year of life and for the total follow-up until 2 years of age.

2. Material and methods

2.1. Study design and participants

A multi-center double blind placebo controlled phase III trial was conducted at Delhi, Pune and Vellore in India between March 11, 2011 and September 26, 2013 [9]. The study was approved by the site Ethics Committees, the Department of Biotechnology (India) and the Western Institutional Review Board (USA), and conducted in compliance with the protocol, good clinical practices, and national regulatory and ethics guidelines. Informed written consent was taken from parents at enrollment.

The detailed methods and study procedures have been previously described [9]. Briefly, a total of 6799 infants were enrolled and randomly assigned in a 2:1 ratio to receive either the vaccine or placebo using the Interactive Voice Response System or Interactive Web Response System with a block size of 12. Enrolled infants were administered the 116E vaccine or placebo along with the childhood vaccines (a pentavalent vaccine including Diphtheria, Pertussis, Tetanus, *Haemophilus influenzae b* and Hepatitis B, and Oral Polio Vaccine) at 6, 10 and 14 weeks of age. Infants were excluded if they had received a rotavirus vaccine, if they had documented immunodeficiency, chronic gastroenteritis or any other disorder that was deemed necessary for exclusion by the investigator. Infants were temporarily excluded if they had any illness needing hospital referral or diarrhea on the day of enrollment.

The 116E vaccine or placebo was administered 5–10 min after administration of 2.5 mL of citrate bicarbonate buffer. Families were contacted weekly at home by trained field workers for ascertaining efficacy and safety outcomes. Trained field workers collected information on characteristics of gastroenteritis episodes for each day. A stool sample was collected for each episode of

gastroenteritis. Mothers were provided mobile phones to ensure easy access to study physicians, who were available round the clock for management of illness. Medical care including transportation and hospitalization were facilitated and paid for by the study [9].

The primary outcome was the incidence of severe RVGE (≥ 11 on the Vesikari scale) [10]. The secondary outcomes being reported include severe RVGE requiring hospitalization or supervised rehydration therapy, very severe RVGE, RVGE of any severity and others.

2.2. Stool sample analysis

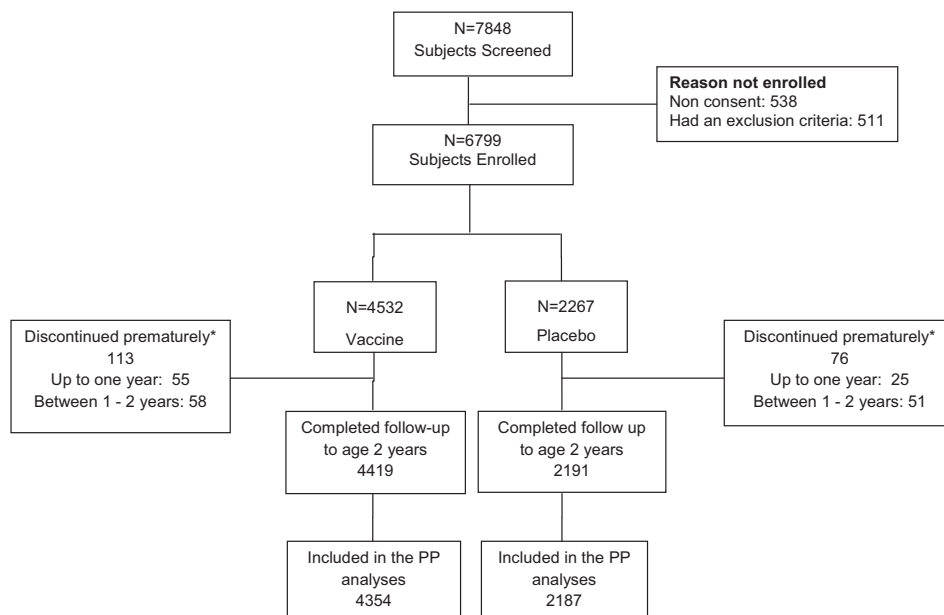
Diarrheal stools were examined for rotavirus with a commercial enzyme immunoassay (Premier Rotaclone, Meridian Bioscience, USA). Rotaclone-positive stools were analyzed for G (VP7) and P (VP4) genotypes by multiplex PCR [11,12]. If both were negative, a PCR assay for the VP6 gene was done to adjudicate where the ELISA result was a false positive [13]. The genotyping assay was not designed to differentiate vaccine G9P[11] from wild G9P[11].

Participants were assessed in detail for intussusception on the basis of broad screening criteria decided *a priori*, described previously [9]. Children with one or more signs or symptoms of the *a priori* criteria were examined by a pediatrician, referred to a pediatric surgeon and admitted to hospital, as necessary. An intussusception case adjudication committee consisting of a pediatric surgeon, a pediatrician, and a radiologist reviewed all investigator-diagnosed cases of intussusception using the Brighton criteria level 1 to provide the final diagnosis [14].

2.3. Statistical analyses

Analyses were done by Quintiles using SAS® Version 9.2. Efficacy analysis is presented for the per-protocol (PP) population. The PP population included all subjects who received the same treatment for all three doses of vaccine or placebo within the *a priori* defined windows and who reported episodes of diarrhea occurring more than 14 days after the third dose. For each endpoint within the three age windows (from more than 14 days after third dose to the end of age 1 and 2 years and for age 1–2 year period), only the first event was counted for each subject. The follow up period associated with each event was calculated as time to occurrence of that event or date of dropout or the date of completion of follow up.

Efficacy estimates for first year of life include events that occurred till one year of age and efficacy for the second year includes events occurring between 1 and 2 years. Vaccine efficacy was calculated as $100 \times (1 - [n_v/F_v]/[n_p/F_p])$ person time incidence rate, where n_v and n_p were the number of subjects with at least one episode in the relevant groups (vaccine or placebo) and F_v and F_p are the total length of follow up in the relevant treatment group. p values and confidence intervals for vaccine efficacy were computed using exact binomial methods [15]. Efficacy outcomes are also displayed as a forest plot of incidence rate ratios on a log scale in the two groups. The time to event analysis by groups are presented as Kaplan–Meier curves.



* The reason discontinued prematurely in the vaccine/placebo group are: Family moved out of study area 58/46, Family refused further participation 25/12.

Death 30/18

Fig. 1. Trial Profile.

2.4. Role of funding sources

The Department of Biotechnology, and Biotechnology Industry Research Assistance Council, Government of India, New Delhi, India; the Bill & Melinda Gates Foundation (#52714) to PATH, USA; Research Council of Norway; Department for International Development, United Kingdom; National Institutes of Health, Bethesda, USA; Bharat Biotech International Limited, Hyderabad, India provided funding. The funders had no influence on how the data was collected; analyses were done by Quintiles.

3. Results

Of the 7848 infants screened, we enrolled 6799 subjects: 4532 subjects received the vaccine and 2267 subjects the placebo. A total of 4419 in the vaccine group and 2191 in the placebo group completed follow up till 2 years of age. In the PP analyses, 4354 in the vaccine group and 2187 in the placebo group were included for the overall analyses (Fig. 1). The total follow up time in the PP population was 7066.4 and 3482.3 years in the vaccine and placebo groups, respectively.

The mean (SD) ages at the time of receiving dose one, two and three were 6.8 (0.6), 11.7 (2.4) and 16.3 (2.8) weeks respectively and these were similar in the vaccine and placebo groups. Compliance to vaccine intake was high for subsequent doses; only 3.5% of infants did not receive all the three intended doses.

3.1. Vaccine efficacy against severe gastroenteritis

Vaccine efficacy in children up to 2 years of age was 55.1% (95% CI 39.9 to 66.4; $p < 0.0001$); the vaccine efficacy in the second year of life of 48.9 (95% CI 17.4 to 68.4; $p = 0.0056$) was only marginally less than that in the first year of life [56.3% (95% CI 36.7 to 69.9; $p < 0.0001$)]. The results were similar in the intent-to-treat (ITT) population where up to 2 years efficacy of 55.8% (95% CI 41.3 to 66.7; $p < 0.0001$) did not differ substantially from that in the first [57.2% (95% CI 38.9 to 70.1; $p < 0.0001$)] or the second year of life at 49%

(95% CI 17.5 to 58.4; $p = 0.0055$). There was no significant interaction of treatment group and site with vaccine efficacy ($p = 0.4802$).

The secondary endpoint analyses strongly supported the primary analysis (Table 1). In the second year of life, the vaccine efficacy against RVGE of any severity requiring hospitalization or supervised rehydration therapy, RVGE requiring hospitalization ≥ 6 h and severe GE of any etiology were 34.3% (95% CI 17.2 to 47.8), 35.9% (95% CI -9.1 to 62) and 10.9 (95% CI -17 to 31.8) respectively. For the genotype specific analysis, there were a total of 199 episodes of severe RVGE that occurred in 195 subjects up to 2 years of age. For this particular analysis, a subject could contribute more than one primary event if associated with a different genotype. Four subjects had more than one episode of severe RVGE with different genotypes; three in the vaccine group and one in the placebo.

The most prevalent (85%) rotavirus genotypes identified in the 199 episodes were G1P[8] (37%; $n = 74$), G2P[4] (31%; $n = 61$), G12P[6] (11%; $n = 21$) and G12P[8] (7%; $n = 13$). A *post hoc* analyses on the genotype specific efficacy is consistent with the overall protective efficacy. The G9P[4] genotype had an imbalance of cases with nine in the vaccine group and one in the placebo group (Table 2).

Survival curves in the vaccine group compared with the placebo group showed a significantly increased cumulative proportion of infants without severe RVGE (Fig. 2). We calculated that 40 infants would need to be immunized to prevent one episode of severe RVGE in the first 2 years of life (95% CI 28.0 to 63.0) and 21 had to be immunized to prevent RVGE of any severity in the same period (95% CI 16.0 to 32.0).

Fig. 3 displays the incidence rate ratios for the primary outcome and several secondary outcomes as a forest plot. In children up to 2 years of age, the incidence of severe RVGE per 100 person years was 1.3 in the vaccine group and 2.9 in the placebo group for an incidence rate ratio of 0.45 (95% CI 0.34 to 0.60) and an absolute rate reduction of 1.6 (95% CI 0.9 to 2.2). In the first year of life, the incidence of severe RVGE per 100 years was 2.0 in the vaccine group and 4.6 in the placebo group, an incidence rate ratio of 0.44 (95% CI 0.30 to 0.63); in the second year of life it was 0.9 in the vaccine

Table 1
Efficacy of the vaccine in the prevention of gastroenteritis in children up to 2 years of age in the per protocol population.

Endpoints	n		Vaccine efficacy % (95% CI)	p value
	VaccineN=4354	PlaceboN=2187		
Severe RV GE				
Till 2 years of age	93 (2%)	102 (5%)	55.1 (39.9 to 66.4)	<0.0001
Till 1 year of age	57 (1%)	65 (3%)	56.3 (36.7 to 69.9)	<0.0001
Between 1 and 2 years of age ^a	38 (<1%)	37 (2%)	48.9 (17.4 to 68.4)	0.0056
Severe RV GE requiring hospitalization ^b or supervised rehydration therapy ^c				
Till 2 years of age	92 (2%)	102 (5%)	55.6 (40.5 to 66.8)	<0.0001
Till 1 year of age	57 (1%)	65 (3%)	56.3 (36.7 to 69.9)	<0.0001
Between 1 and 2 years of age ^a	37 (<1%)	37 (2%)	50.2 (19.3 to 69.3)	0.0042
Very severe RV GE				
Till 2 years of age	12 (<1%)	14 (<1%)	57.2 (0.3 to 81.9)	0.0491
Till 1 year of age	9 (<1%)	9 (<1%)	49.8 (-42.6 to 82.4)	0.2176
Between 1 and 2 years of age ^a	3 (<1%)	5 (<1%)	70.1 (-53.9 to 95.4)	0.1750
RV GE of any severity				
Till 2 years of age	406 (9%)	310 (14%)	36.4 (26.0 to 45.3)	<0.0001
Till 1 year of age	226 (5%)	172 (8%)	35.0 (20.2 to 46.9)	<0.0001
Between 1 and 2 years of age ^a	194 (4%)	150 (7%)	36.2 (20.5 to 48.7)	<0.0001

Data are n (%) unless otherwise indicated. We define severe gastroenteritis as episodes with a Vesikari score of 11 or greater. Episodes of severe rotavirus gastroenteritis had a Vesikari score of 11 or greater and presence of rotavirus (Rotaclone positive and VP6 or VP4 and VP7 positive by RT PCR) strains; includes all cases except those for which G9P[11] was isolated. Episodes of very severe gastroenteritis had a Vesikari score of 16 or greater.

^a N in vaccine = 4339, placebo = 2177.

^b Inpatient admission for at least 6 h in a treatment facility or hospital.

^c Administration of oral rehydration salts or intravenous fluids.

group and 1.7 in the placebo group, an incidence rate ratio of 0.51 (95% CI 0.32 to 0.83).

3.1.1. Safety

Studies have reported adverse events immediately after vaccination and in the 2 week window following any of the three doses [9]. We observed serious adverse events at the same rates in the vaccine (20.9%, n=947) and placebo group (22.7%, n=515). Only three subjects, one in the vaccine (urticaria) and two in the placebo (acute gastroenteritis and suspected sepsis) group had a serious adverse event (SAE) that was considered related to the

vaccine. There were no statistically significant differences in system organ class and preferred terms as classified by MedDRA except for rotavirus gastroenteritis which was lower in the vaccine group as expected. There were 30 deaths in 4532 (0.7%) vaccine group and 18 in the 2267 (0.8%) placebo group and none were considered related to the vaccine.

Intussusception by Brighton Level 1 criteria was met in 8 of the 4532 (0.2%) events occurring in vaccine group and 3 of the 2267 (0.1%) events occurring in the placebo group (p=0.7613). None occurred within 30 days of a vaccine dose and all were reported only after the third dose. The intussusception events following the

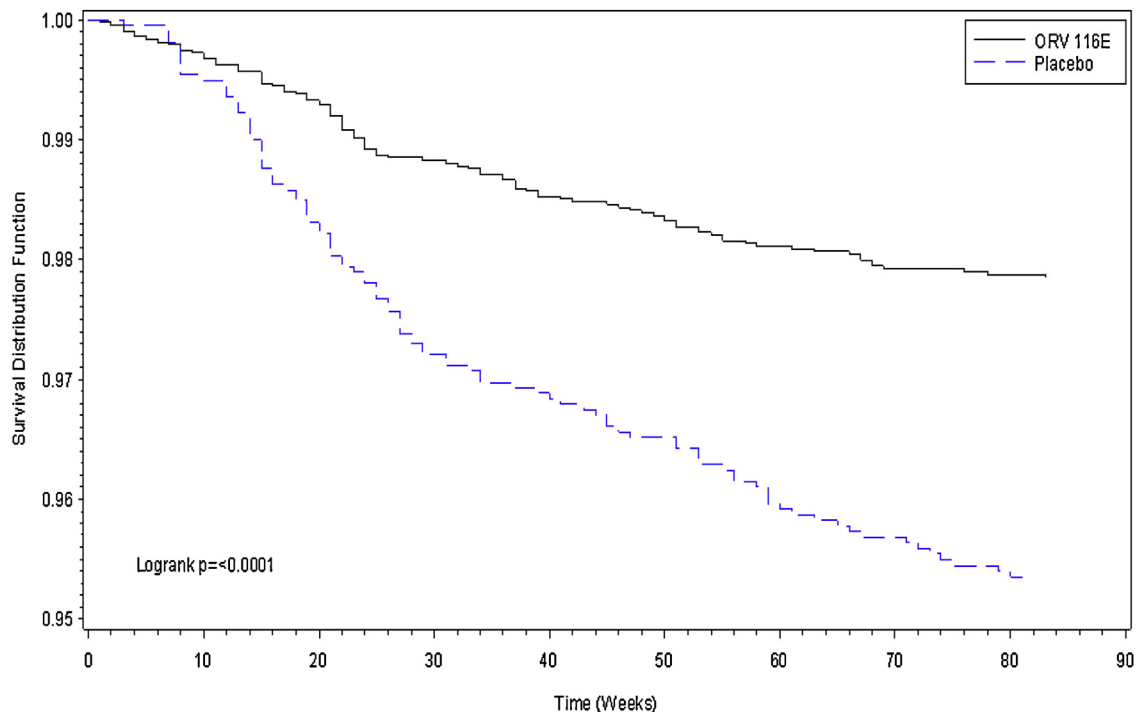


Fig. 2. Kaplan–Meier survival curve for severe rotavirus gastroenteritis per protocol population: time 0 represents 15 days after receipt of the third dose of vaccine or placebo.

Table 2
Efficacy analysis for severe rotavirus gastroenteritis by genotype in per protocol population up to 2 years of age.

	Vaccine N=4354	Placebo N=2187	Vaccine efficacy % (95% CI)
All ^a	93 (2.1%)	102 (4.7%)	55.1% (39.9 to 66.4)
G1P[8]	40 (0.9%)	34 (1.6%)	42.0% (5.6 to 64.2)
G2P[4]	26 (0.6%)	35 (1.6%)	63.4% (37.4 to 78.8)
G12P[6]	8 (0.2%)	13 (0.6%)	69.7% (21.1 to 89.1)
G12P[8]	5 (0.1%)	8 (0.4%)	69.2% (–6.8 to 92.1)
G9P[4]	9 (0.2%)	1 (<0.1%)	–343.5% (–19562 to 38.5)
Others ^b	8 (0.2%)	12 (0.5%)	67.1% (12.6 to 88.4)

Data are n (%) unless otherwise indicated.

^a Total number of subjects included in PP population is 195; 4 subjects had more than 1 episode of severe non vaccine RV GE and therefore the total number of episodes 199 is greater than the total number of subjects.

^b Includes all genotypes causing seven cases or less (G9P[8], G1P[4], G1P[6], G2P[6], G1P[0], G0P[0], G9P[0], G12P[11]).

third dose occurred between 112 and 587 days post vaccination in the vaccine group and between 36 and 605 days in the placebo group.

4. Discussion

The efficacy of the 116E vaccine against the primary outcome, severe RVGE, in the second year of life (48.9%) is only marginally lower than the 56.3% reported in the first year of life [9]. The findings for the second year follow up from the ITT analyses support the PP analyses. The protection offered in the second year of life by the 116E vaccine increased with greater severity of clinical disease, just as was seen in the first year analyses [9].

In developing countries, the point estimate for efficacy against severe RVGE during the first 2 years of life for the 116E vaccine is comparable to results reported for the two licensed vaccines, RotaTeq and Rotarix [16]. While the efficacy of rotavirus vaccines

has been lower in the second than the first year of life, the reduction in efficacy was substantially lower in some settings with licensed vaccines [3,4,17,18]. In this regard, only a marginal decrease in efficacy of 116E in the second compared to the first year of life is reassuring. In the updated analyses for the first 2 years of life, SAEs, deaths and cases of intussusception were similar between vaccine and placebo groups. A decisive assessment of the risk of intussusception is to be carried out during phase IV post marketing studies.

As noted previously, the 116E vaccine has an unusual G9P[11] genotype that is rarely associated with clinical disease in India or other countries. The protection offered by this vaccine during the first 2 years of life is against the array of commonly circulating genotypes including G1P[8], G2P[4], G12P[6], G12P[8] and G9P[4]. This suggests that the vaccine could offer significant protection in varying geographical settings and over time. This finding also supports the view that there are multiple determinants that provide a lead to protective immunity. We noted an imbalance of cases associated with G9P[4] but could not identify any biological basis for this imbalance and conclude that this was due to chance alone.

The efficacy of the licensed rotavirus vaccines is higher in developed than in developing countries [19–23]. Although the efficacy of 116E in the first 2 years of life is modest as it is for other licensed vaccines, the impact on preventing deaths related to severe RVGE is likely to be high in India and other developing countries because of the higher disease burden [2,4]. It is for this reason that the World Health Organization has recommended inclusion of rotavirus vaccine into national immunization programs.

Finally, the development of 116E is a unique example of team work and global collaboration and represents a novel approach to development of affordable health technologies of particular interest to developing countries [24]. Efforts are underway to understand the reasons underlying the relatively modest efficacy of all live rotavirus vaccines in low middle income countries.

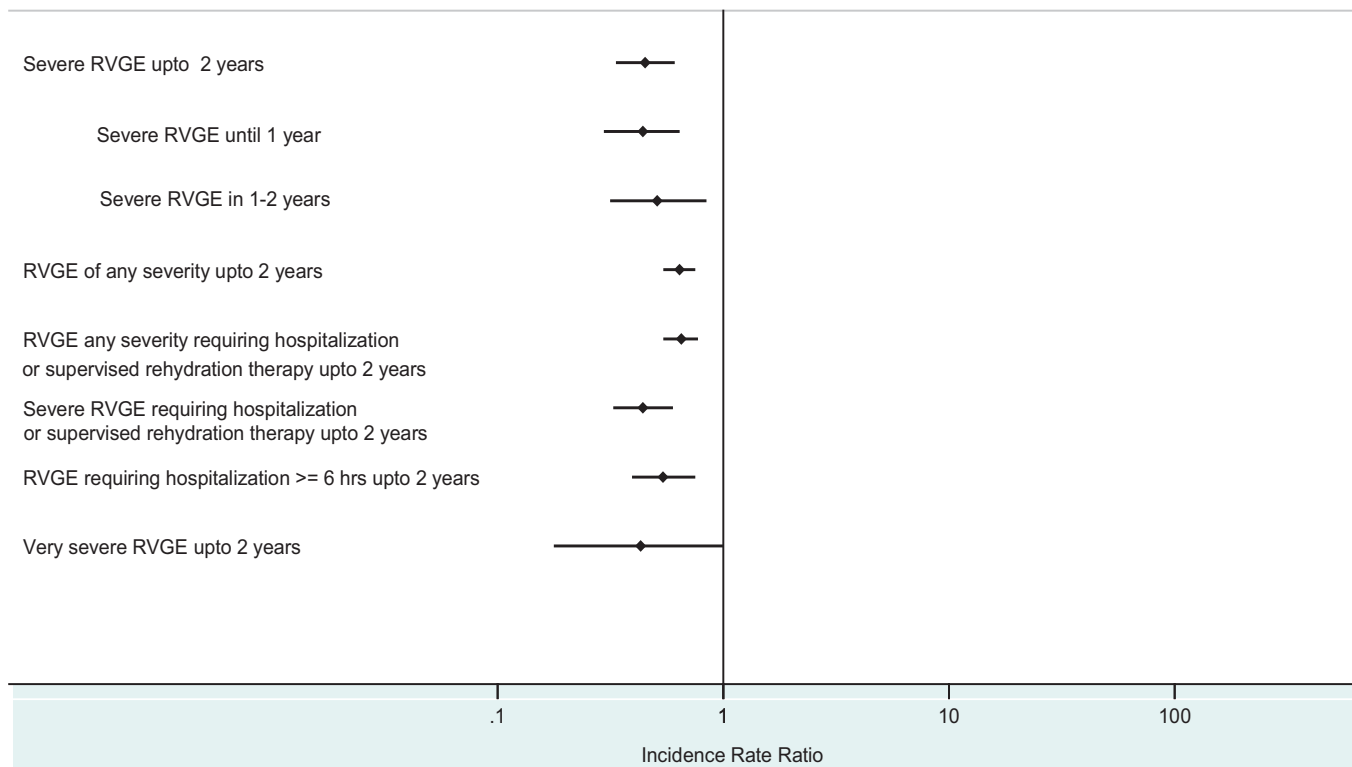


Fig. 3. Forest plot of incidence rate ratio on log scale by case definition: efficacy PP population.

Contributors

NB, JB and MKB prepared the manuscript and all authors reviewed and approved. TRC, AB, JJ, NG, AK, GK, SSR, SJ, JM, AA, HS, VA for design of protocol, trial implementation strategy and conduct. NB, KA and ST contributed to the design of protocol, trial implementation strategy, oversight of trial conduct and data analyses. JB, MKB, GT, RG, HBG, GC, TSR contributed to the trial design and interpretation of data and laboratory guidance. KM, GVJAH, SP for product development. MP, RK contributed to data analyses. SV for analyses of specimens.

All authors have approved the final manuscript.

Conflict of interest

KM, GVJAH and SP are employees of Bharat Biotech International Limited. Other authors have no conflict of interest.

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Sponsor: Bharat Biotech International Limited, Genome Valley, Andhra Pradesh, India.

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