Vaccine 40 (2022) 2184–2190

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Safety and reactogenicity of a liquid formulation of human rotavirus vaccine (porcine circovirus-free): A phase III, observer-blind, randomized, multi-country study

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ARTICLE INFO

Article history:
Received 2 November 2021
Received in revised form 15 February 2022
Accepted 17 February 2022
Available online 26 February 2022

Keywords:
Human rotavirus vaccine
Liquid
Porcine circovirus-free
Infant
Safety
Reactogenicity

ABSTRACT

Background: The introduction of rotavirus vaccines in national immunization programs has decreased mortality and hospitalizations due to diarrhea. GSK's live-attenuated, human rotavirus vaccine (HRV) is a 2-dose vaccine for oral administration. Following the detection of porcine circovirus type 1 (PCV-1) in HRV, a PCV-free (no detection of PCV-1 and PCV-2 according to the detection limits of tests used) HRV was developed. The immunogenicity, reactogenicity and safety of a liquid (liq) PCV-free HRV were assessed in two prior studies. The present study aimed to generate additional reactogenicity and safety data.

Methods: This phase III, observer-blind, randomized, controlled multi-country study enrolled healthy 6–12-week-old infants. Infants were randomized to receive 2 doses of either the liq PCV-free HRV (N = 677) or the lyophilized (lyo) HRV (N = 674) 1–2 months apart. Solicited adverse events (AEs) were recorded for 8 days after each dose, unsolicited AEs for 31 days and serious AEs (SAEs) from dose 1 until the end of the 6-month safety follow-up.

Results: The occurrence of solicited general AEs was comparable between the liq PCV-free HRV and the lyo HRV groups, with irritability/fussiness being the most frequently reported (74.9% [95% confidence interval: 71.4–78.1] and 72.1% [68.6–75.5]). Unsolicited AEs were reported for 29.7% (26.3–33.3) and 30.6% (27.1–34.2) of infants in the liq PCV-free HRV and the lyo HRV group. A total of 39 and 38 infants reported at least one SAE, respectively. The most common SAEs were upper respiratory tract (0.7% and 0.9%) and urinary tract infections (0.9% and 0.6%). One SAE (constipation) in the liq PCV-free HRV group

Abbreviations: AE, adverse event; $CCID_{50}$, cell culture infective dose; CI, confidence interval; COVID-19, coronavirus disease 2019; HRV, human rotavirus vaccine; IDMC, independent data monitoring committee; LAR, legally acceptable representative; liq, liquid; lyo, lyophilized; MedDRA, Medical Dictionary for Regulatory Activities; PCV, porcine circovirus; RV, rotavirus; SAE, serious adverse event; US, United State.

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https://doi.org/10.1016/j.vaccine.2022.02.065
0264-410X/

was considered as potentially causally related to vaccination by the investigator. No deaths were reported.
Conclusions: The study showed that the reactogenicity and safety profiles of the liq PCV-free HRV and the lyo HRV are similar.
ClinicalTrials.gov identifier: NCT03954743.

1. Introduction

In 2016, diarrhea was the fifth leading cause of death in children < 5 years of age, with rotavirus (RV) being the main etiologic agent [1]. The majority of diarrhea-related deaths occur in resource-limited countries, but diarrhea also causes considerable morbidity worldwide [1]. RV vaccines have been introduced in national immunization programs of many countries, which has led to a decrease in mortality and hospitalizations due to diarrhea [1,2].

The live-attenuated human RV vaccine (HRV; *Rotarix*; GSK) is a 2-dose oral vaccine; the first dose should be given from 6 weeks of age and the second dose before 24 weeks of age [3]. The lyophilized (lyo) and liquid (liq) formulations of the HRV vaccine were shown to be efficacious and immunogenic with acceptable safety profiles in large-scale, randomized, controlled trials in multiple countries [4–10].

In 2010, porcine circovirus type 1 (PCV-1) material was unexpectedly detected in HRV, and PCV-1 and PCV-2 material was found in the human-bovine reassortant RV vaccine (*RotaTeq*; Merck) [11,12]. The detection of PCV-1 material in HRV led to further investigations into the nature, amount and source of this contamination. Although these investigations did not detect any safety risk to immunized children [11], GSK developed a PCV-free HRV as a commitment to Regulatory Authorities [11,13]. A phase III, randomized clinical trial that enrolled 1612 infants was conducted in Costa Rica, Finland, Germany, Japan, the Republic of Korea, Spain, Taiwan and the United States (US) and demonstrated lot-to-lot consistency of the liq PCV-free HRV. The study also showed that the immune response elicited by the liq PCV-free HRV was non-inferior to that induced by the lyo HRV, and that both formulations had similar reactogenicity and safety profiles [13]. A subsequent study including 1272 vaccinated US infants showed that routine pediatric vaccines induced non-inferior immune responses and had comparable safety profiles when co-administered with the liq PCV-free HRV compared to when co-administered with the lyo HRV [14]. The current study was conducted to generate additional reactogenicity and safety data in the PCV-free HRV vaccine development plan.

2. Methods

2.1. Study design, participants and vaccines

This was a phase III, observer-blind, randomized, controlled study conducted in 37 centers in five countries/regions (Canada, Hong Kong, Taiwan, Turkey and the US) between July 19, 2019 and November 30, 2020 (ClinicalTrials.gov: NCT03954743).

Participants were healthy infants (girls and boys), 6–12 weeks of age, who had not previously received any RV vaccine, had no history of confirmed RV gastroenteritis or any immunosuppressive condition, and for whom parents or legally acceptable representatives (LARs) had provided written informed consent. The complete list of inclusion and exclusion criteria is provided in **Supplementary material 1**. Infants were randomly allocated to two parallel groups (1:1) using GSK's central internet randomization system. The randomization algorithm used a minimization procedure with center and country as minimization factors, each with an equal weight. The randomization system determined the study group at first dose and provided the treatment number for each dose. One group received 2 oral doses of the liq PCV-free HRV and the other group received 2 oral doses of the lyo HRV, 1–2 months apart. As the liq HRV formulation was not licensed in the US at the time of the study conduct, the lyo HRV formulation was used as a control. Concomitant administration of routine childhood vaccines (including vaccines against tuberculosis, diphtheria, pertussis, tetanus, hepatitis B, *Haemophilus influenzae* type b, polio [inactivated], *Neisseria meningitidis* and *Streptococcus pneumoniae*) was allowed according to the local immunizaton practices in each participating country/region.

Three study visits were planned: at day 1 (administration of dose 1), month 1–2 (administration of dose 2) and month 2–4 (follow-up, 1–2 months after dose 2). For each infant, the total duration of the study was approximately 7–8 months, including a 6-month extended safety follow-up period after the last dose of the HRV vaccine. The study followed the prevailing triage policy and infection control measures required for coronavirus disease 2019 (COVID-19) at all study sites. The study was observer-blind; the personnel involved in vaccine preparation and administration was not involved in the clinical evaluation.

One dose of the liq PCV-free HRV had a volume of 1.5 ml and contained ≥ 6.0 $\log_{10}$ cell culture infective dose ($CCID_{50}$) of the live attenuated HRV RIX4414 strain. PCV-free was defined as no detection of PCV-1 and PCV-2 according to the limit of detection of the tests used [13]. The lyo HRV was reconstituted with a $CaCO_3$-based diluent to a volume of 1 ml and contained ≥ 6.0 $\log_{10}$ $CCID_{50}$ of the live attenuated HRV RIX4414 strain.

The study protocol, protocol amendments, informed consent form and other study-related documents were reviewed and approved by the relevant institutional review boards and independent ethics committees. The study was conducted in accordance with the protocol and with ethical principles that have their origin in the Declaration of Helsinki, applicable International Conference on Harmonization Good Clinical Practice Guidelines and applicable laws and regulations.

The protocol is available at https://www.gsk-studyregister.com/en/trial-details/?id=208236.

2.2. Objectives

The primary objectives were to evaluate the reactogenicity (in terms of solicited adverse events [AEs] during the 8 days following each HRV vaccination) and safety (in terms of unsolicited AEs during the 31 days following each vaccination and serious AEs [SAEs] during the entire study period) of the liq PCV-free HRV and the lyo HRV.

2.3. Reactogenicity and safety assessment

Solicited and unsolicited AEs were collected using diary cards, completed by the infants' parents/LARs after each vaccine dose

and returned at the next study visit. The infants' parents/LARs were also instructed to measure and record the oral, axillary or rectal body temperature. All SAEs (defined as untoward medical occurences that resulted in disability/incapacity, required [prolongation of] hospitalization, were life-threatening or resulted in death) were immediately recorded and reported to the sponsor via an electronic expedited AE reporting form.

Solicited general AEs were reported during the 8 days following HRV vaccination (i.e., on the day of vaccination and 7 subsequent days). Unsolicited AEs were reported during the 31 days following HRV vaccination (i.e., on the day of vaccination and 30 subsequent days). SAEs and AEs/SAEs leading to withdrawal were reported from the first HRV vaccination to study end. The following solicited general AEs were assessed: cough/runny nose, diarrhea (defined as passage of three or more looser than normal stools within a day), fever (defined as temperature ≥ 38.0 °C/100.4°F), irritability/fussiness, loss of appetite and vomiting (defined as one or more episodes of forceful emptying of partially digested stomach contents ≥ 1 h after feeding within a day). The intensity of each AE was graded from 1 (mild) to 3 (severe). Definitions of grade 3 AEs were: ≥6 looser than normal stools per day for diarrhea, ≥3 episodes of vomiting/day, temperature > 39.5 °C/103.1°F for fever, not eating at all for loss of appetite, crying inconsolably or preventing normal activity for irritability/fussiness, cough/runny nose that prevented everyday activities and an AE that prevented normal, everyday activities for all unsolicited AEs.

Medically attended solicited and unsolicited AEs were defined as symptoms or illnesses requiring hospitalization, an emergency room visit or an unscheduled visit to/by a health care provider. The relationship between the study vaccines and the occurrence of each AE/SAE was assessed by the investigators.

The reports of unsolicited AEs were reviewed by the investigators, and the signs and symptoms were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Every verbatim term was matched with the appropriate system organ class and preferred term.

An independent data monitoring committee (IDMC) consisting of clinical experts and a biostatistician reviewed the unblinded safety data on a regular basis to evaluate if there was any safety concern with the liq PCV-free HRV.

2.4. Statistical analyses

The target enrollment was 1350 infants (675 in each group). All analyses were descriptive and were performed using SAS Life Sciences Analytics Framework 5.2.2. Safety was evaluated in the exposed set of infants (i.e., all infants who received at least 1 dose of the study vaccine). The percentages of doses and of infants with at least one solicited general AE during the 8 days following HRV vaccination were calculated along with exact 95% confidence intervals (CIs). The same calculations were performed for grade 3 solicited general AEs, solicited general AEs assessed as causally related to vaccination, grade 3 solicited general AEs assessed as causally related to vaccination and solicited general AEs requiring medical attention. For fever, additional analyses were performed by 0.5 °C increments. These calculations were also performed by sex. The percentages of infants with unsolicited AEs, grade 3 unsolicited AEs, unsolicited AEs assessed as causally related to vaccination, grade 3 unsolicited AEs assessed as causally related to vaccination and unsolicited AEs requiring medical attention during the 31 days following HRV vaccination were calculated, along with exact 95% CIs. The percentages of infants who experienced at least one SAE during the entire study were calculated per study group, and all SAEs were tabulated.

3. Results

3.1. Study participants

A total of 1351 infants were enrolled and received at least 1 dose of the study vaccine (exposed set). Of the 677 infants in the liq PCV-free HRV group, 663 (97.9%) received 2 doses. Of the 674 infants in the lyo HRV group, 657 (97.5%) received 2 doses. A total of 1310 infants completed the study (653 in the liq PCV-free HRV and 657 in the lyo HRV group). The most common reason for withdrawal was 'consent withdrawal, not due to an AE', with 1.9% and 1.8% of infants in the liq PCV-free HRV and the lyo HRV group, respectively (Fig. 1). Protocol deviations were recorded for 10% of infants in each group.

Other childhood vaccines were co-administered with dose 1 (i.e., administered on the same day) in 299 infants (44.2%) in the liq PCV-free HRV and 291 infants (43.2%) in the lyo HRV group. Co-administration with dose 2 was reported for 288 infants (43.4%) and 280 infants (42.6%), respectively.

The mean age of the infants at first dose was 9.0 weeks for both groups. Approximately half of the infants were girls, and most were White or Asian. Overall, the baseline characteristics were comparable between the two groups (Table 1).

3.2. Reactogenicity and safety

During the 8-day post-vaccination periods, at least one solicited or unsolicited AE was reported for 85.2% and 82.5% of infants in the liq PCV-free HRV and the lyo HRV group, respectively.

3.2.1. Solicited adverse events

Overall compliance in completing solicited AE information was high, with 98.7% in the liq PCV-free HRV and 99.1% in the lyo HRV group. The occurrence of solicited general AEs was comparable between the two groups and similar after each dose (Fig. 2**; Supplementary material 2**). Most solicited AEs were mild or moderate. Irritability/fussiness was the most frequently reported solicited general AE in both groups, reported for 74.9% (95% CI: 71.4–78.1) and 72.1% (95% CI: 68.6–75.5) of infants after at least 1 dose in the liq PCV-free HRV and the lyo HRV group, respectively. It was also the most common grade 3 solicited AE (9.7% [95% CI: 7.6–12.2] and 7.1% [95% CI: 5.3–9.3]) (Fig. 2**; Supplementary material 2, Table S2.4**). Cough/runny nose was the most frequently reported solicited general AE leading to medically attended visits in both groups (3.0% [95% CI: 1.8–4.5] in the liq PCV-free HRV and 2.7% [95% CI: 1.6–4.2] in the lyo HRV group) (**Supplementary material 2, Table S2.4**). Solicited general AEs were reported with comparable frequencies in girls and boys in both groups (**data not shown**).

3.2.2. Unsolicited adverse events

At least one unsolicited AE was reported in 29.7% (95% CI: 26.3–33.3) and 30.6% (95% CI: 27.1–34.2) of infants in the liq PCV-free HRV and the lyo HRV group (Table 2). Grade 3 unsolicited AEs were reported in 1.2% (95% CI: 0.5–2.3) and 1.6% (95% CI: 0.8–2.9) of infants, respectively (Table 2). The reported unsolicited and grade 3 unsolicited AEs are presented in **Supplementary material 3, Tables S3.1 and S3.2.** For 2.5% (95% CI: 1.5–4.0) of infants in the liq PCV-free HRV and 4.5% (95% CI: 3.0–6.3) of infants in the lyo HRV group, unsolicited AEs that were considered causally related to the vaccines by the investigator were reported, with 0.3% (95% CI: 0.0–1.1) and 0.4% (95% CI: 0.1–1.3) of infants having grade 3 vaccine-related unsolicited AEs (Table 2; **Supplementary material 3, Tables S3.3 and S3.4**). Unsolicited AEs requiring medical atten-

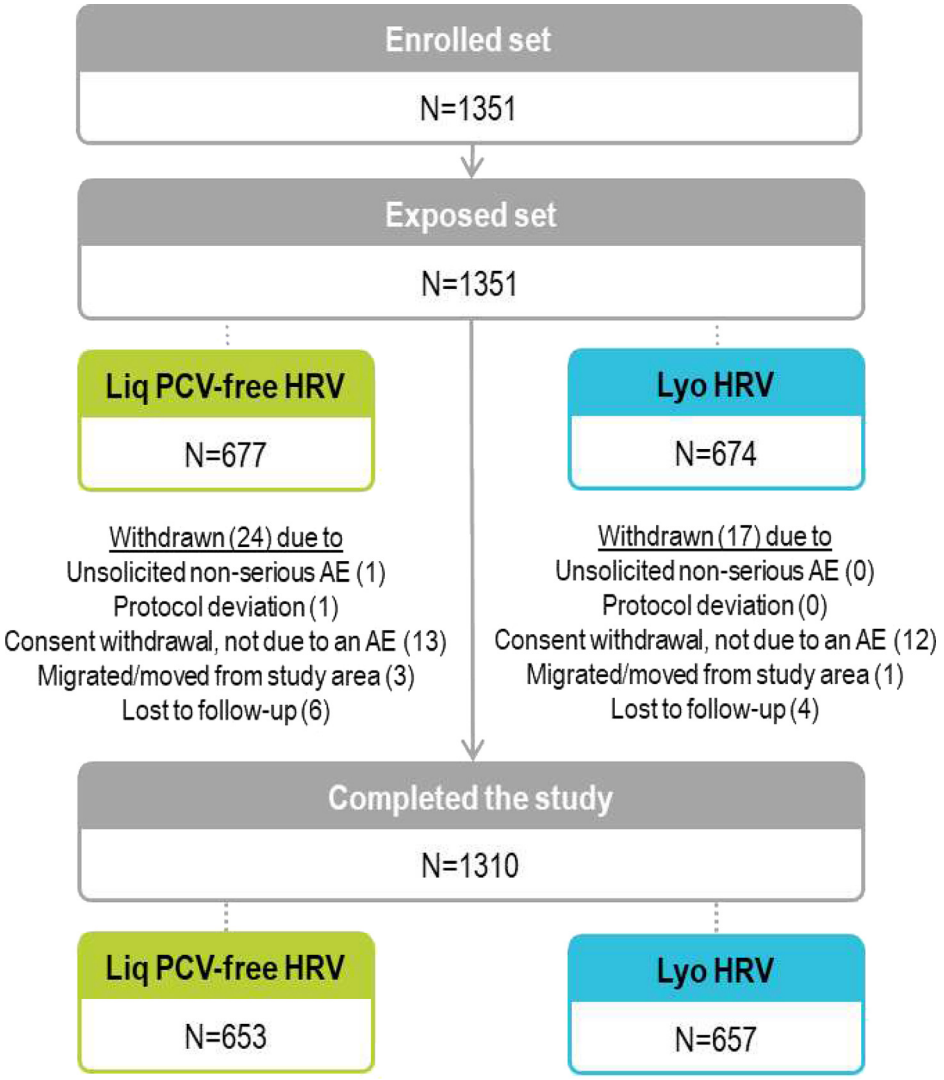

Fig. 1. Flow of participants N, number of infants; liq, liquid; PCV, porcine circovirus; HRV, human rotavirus vaccine; lyo, lyophilized; AE, adverse event.

tion were reported for 16.1% (95% CI: 13.4–19.1) of infants in the liq PCV-free HRV and for 20.3% (95% CI: 17.3–23.6) of infants in the lyo HRV group (Table 2; **Supplementary material 3, Table S3.5**).

One infant who received the liq PCV-free HRV was withdrawn due to an unsolicited AE. Ten days after receiving the first dose, the infant was diagnosed with mild hematochezia, assessed as related to the vaccine by the investigator. Blood was found in stool once, and stools were normal afterwards. Physical examination, abdominal ultrasound and blood tests showed no abnormalities.

3.2.3. Serious adverse events

A total of 62 SAEs were reported in 39 infants (5.8%) in the liq PCV-free HRV group. In the lyo HRV group, 59 SAEs were reported in 38 infants (5.6%) (Table 2). The most common SAEs were upper respiratory tract infections (0.7% and 0.9% of infants in the liq PCV-free HRV and the lyo HRV group, respectively) and urinary tract infections (0.9% and 0.6%). A complete list of SAEs is presented in **Supplementary material 3, Table S3.6**. One SAE (constipation) in an infant immunized with the liq PCV-free HRV was considered by the investigator as potentially causally related to vaccination. The constipation started 6 days after receiving the first dose and was of mild intensity. The infant was hospitalized due to a lack of bowel output for 4 days and reduced oral intake. Abdominal radiographs revealed no dilated bowels 3 days after onset, and the infant was discharged 4 days after onset. This SAE resolved 14 days after onset. There were no reported cases of intussusception or deaths in the study.

4. Discussion

The present study showed that the reactogenicity and safety profiles of the liq PCV-free HRV were comparable to the lyo HRV. This finding is consistent with the results from two previous studies that compared these two formulations [13,14]. The first study demonstrated the immunological non-inferiority of the liq PCV-free HRV compared to the lyo HRV [13]. The second study demonstrated that childhood vaccines (the diphtheria-tetanus-acellular pertussis, hepatitis B and inactivated poliovirus combination vaccine, the tetanus toxoid-conjugated vaccine against *Haemophilus influenzae* type b and the 13-valent pneumococcal conjugate vaccine) co-administered with the liq PCV-free HRV induced non-inferior immune responses compared to those after co-administration with the lyo HRV [14].

Table 1
Baseline characteristics (exposed set).

	Liquid PCV-free HRV (N = 677[a])	Lyophilized HRV (N = 674[a])
Age at dose 1, weeks		
Mean ± SD	9.0 ± 1.5	9.0 ± 1.5
Median (min–max)	9.0 (6–13)	9.0 (5–13)
Age at dose 2, weeks		
Mean ± SD	16.7 ± 2.6	16.9 ± 2.7
Median (min–max)	17.0 (10–23)	17.0 (10–29)
Mean gestational age ± SD, weeks	38.5 ± 1.5	38.5 ± 1.5
Mean height at dose 1 ± SD, cm	58.1 ± 2.8	58.2 ± 2.9
Mean weight at dose 1 ± SD, kg	5.4 ± 0.8	5.4 ± 0.7
Female, n (%)	336 (49.6)	357 (53.0)
Race, n (%)		
American Indian or Alaska Native	2 (0.3)	1 (0.1)
Asian	302 (44.6)	301 (44.7)
Black or African American	14 (2.1)	10 (1.5)
Native Hawaiian or Other Pacific Islander	0 (0.0)	2 (0.3)
White	339 (50.1)	346 (51.3)
Other	20 (3.0)	14 (2.1)
Country/region, n (%)		
Canada	122 (18.0)	117 (17.4)
Hong Kong	182 (26.9)	182 (27.0)
Taiwan	107 (15.8)	108 (16.0)
Turkey	137 (20.2)	138 (20.5)
United States	129 (19.1)	129 (19.1)

PCV, porcine circovirus; HRV, human rotavirus vaccine; N, number of infants; SD, standard deviation; n (%), number (percentage) of infants in a given category.
[a] N was 663 (liq PCV-free HRV group) and 657 (lyo HRV group) for age at dose 2.

The reactogenicity and safety profiles of the original lyo and liq formulations of HRV (in which PCV-1 material was detected in 2010) were previously evaluated in comparison to placebo in an integrated analysis combining data of 28 randomized, placebo-controlled, double-blind phase II and III trials [15]. This integrated analysis included over 100 000 infants worldwide and showed that the reactogenicity and safety profiles of the HRV vaccine were acceptable and comparable to those of the placebo. The incidence of solicited general AEs was similar following HRV vaccine or placebo administration, with reports of at least one solicited general AE for 79.7% and 77.7% of infants, respectively. For unsolicited AEs, these percentages were 47.8% and 49.4%, respectively, and for SAEs 2.1% and 2.3% [15].

A transient increase in the risk of intussusception mostly within 7 days after oral rotavirus vaccine administration has been reported previously, though available data confirm that the documented benefits of rotavirus vaccination by far outweigh the risk [16]. No cases of intussusception were reported in the present study.

Because the present study was impacted by the COVID-19 pandemic, measures were taken to allow more flexibility for the collection of safety data (e.g., safety follow-up by telephone call or transmission of diary cards by electronic means) while ensuring the welfare and safety of the infants, leading to a high retention rate.

The present study had some limitations as it was descriptive with a limited sample size. Also, although the study population was diverse, it mainly included infants from two racial backgrounds (White and Asian) from five countries/regions (Canada, Hong Kong, Taiwan, Turkey and the US) thus potentially limiting generalizability to other populations.

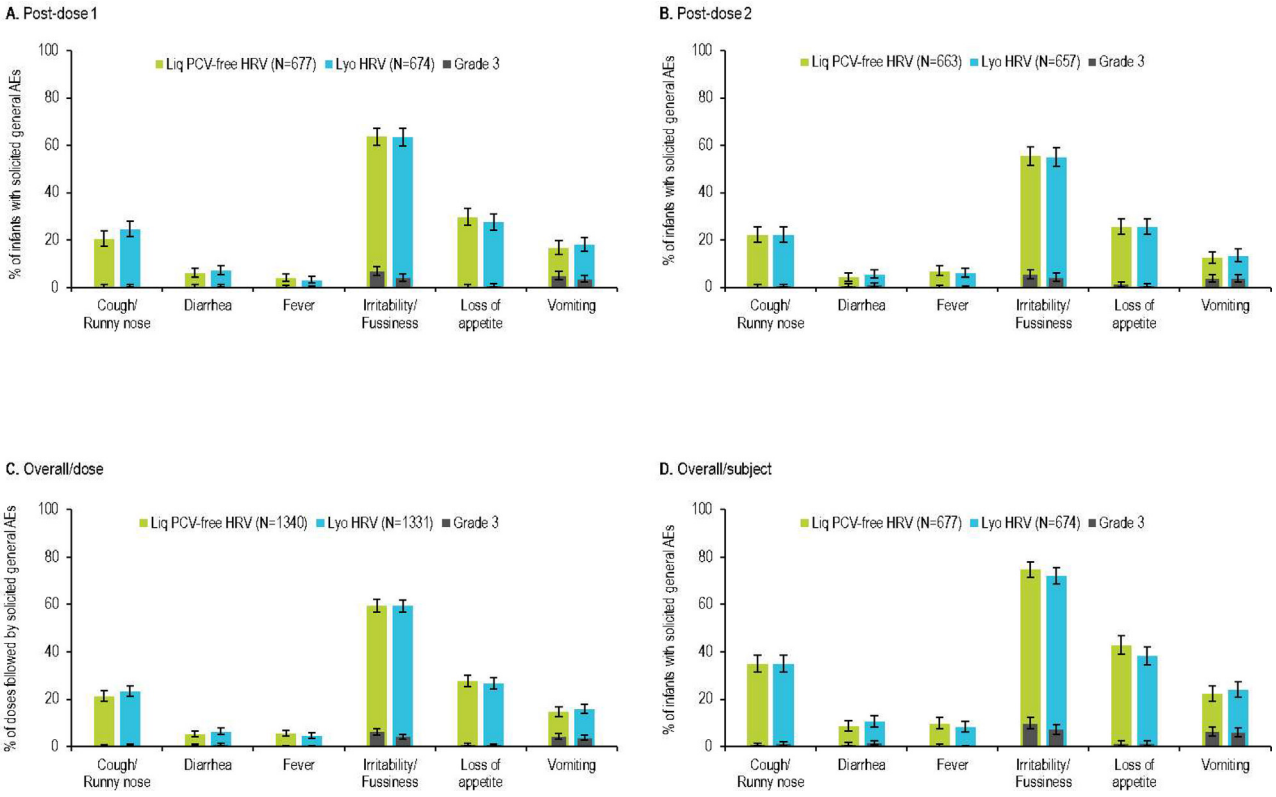

Fig. 2. Solicited general adverse events during the 8 days following HRV vaccination (exposed set). AE, adverse event; liq, liquid; lyo, lyophilized; PCV, porcine circovirus; HRV, human rotavirus vaccine; N, number of infants. Error bars represent 95% confidence intervals.

Table 2
Unsolicited adverse events during the 31 days following HRV vaccination and serious adverse events from first study vaccination up to study end (exposed set).

	Liquid PCV-free HRV (N = 677)		Lyophilized HRV (N = 674)	
	n	% (95% CI)	n	% (95% CI)
Any unsolicited adverse events	201	29.7 (26.3–33.3)	206	30.6 (27.1–34.2)
Grade 3	8	1.2 (0.5–2.3)	11	1.6 (0.8–2.9)
Causal relationship to vaccination	17	2.5 (1.5–4.0)	30	4.5 (3.0–6.3)
Grade 3	2	0.3 (0.0–1.1)	3	0.4 (0.1–1.3)
Requiring medical attention	109	16.1 (13.4–19.1)	137	20.3 (17.3–23.6)
Any serious adverse events	39	5.8 (-)	38	5.6 (-)

PCV, porcine circovirus; HRV, human rotavirus vaccine; N, number of infants; n/%, number/percentage of infants in a given category; CI, confidence interval.

5. Conclusions

The present study showed similar reactogenicity and safety profiles for the liq PCV-free HRV and the lyo HRV. These results support the acceptable safety profile of the liq PCV-free HRV.

6. Trademark statement

Rotarix is a trademark owned by or licensed to the GSK group of companies. *RotaTeq* is a trademark of Merck.

7. Author contributions

All authors participated either in the design (CCH, LM, TS, TFL), collection (BSC, BT, CCH, DB, CCD, JDC, LMH, MT, SH, TS, TFL, YLL), implementation (BSC, BT, CCH, DB, ECD, JDC, LMH, MT, SH, TFL, YLL) or analysis and interpretation of data (DB, JDC, LM, LMH, MP, SH, TS, TFL) of the study as well as in the development of this manuscript. All authors had full access to the data and granted their final approval of the manuscript before submission. All authors attest they meet the ICMJE criteria for authorship.

8. Funding sources

GlaxoSmithKline Biologicals SA covered all costs associated with the development and publishing of the present manuscript.

9. Declaration of Competing Interest

DB, LM, MP and TS are employees of the GSK group of companies, and DB, LM and TS hold shares in the GSK group of companies as part of their employee remuneration. BT, ECD, JDC, SAH and YLL received grants from the GSK group of companies during the conduct of the study. BT's institution received research grants for vaccine-related studies from Merck, GSK and Pfizer. SAH declares other financial relationships with Sanofi, Pfizer, Merck, Entos, IMV Inc. and VBI Vaccines outside of the submitted work. SAH declares having served on a data safety monitoring board for Medicago, advisory boards for Pfizer, Merck, GSK, Sanofi, AstraZeneca, Moderna, Medicago, and has received payment for expert testimony from the Province of Ontario, Canada. Additionally, SAH serves as a co-chair of the Vaccine Surveillance Reference Group, Public Health Agency of Canada. ECD declares other financial relationships with Sanofi Pasteur, Pfizer and the GSK group of companies outside of the submitted work. BSC, CCH, LMH, MT and TFL have no competing interest to declare. The authors have no non-financial competing interest to declare.

Acknowledgements

The authors thank all participants involved in the study, study nurses, coordinators and study investigators. The authors are grateful to Meda Kondolot (Erciyes University Faculty of Medicine, Turkey) for her contribution to the study. The authors are grateful to the members of the Independent Data Monitoring Committee: Carlo Giaquinto, Shabir Madhi, Nigel Cunliffe, Catherine Legrand and Dennis Conrad for providing a valuable contribution in the review of the safety data.

The authors would also like to thank Tina Van den Meersche and Manuel Zocco (Modis c/o GSK) for medical writing support and manuscript coordination.

Rota-096 group members.

The authors would like to thank the Rota-096 study group including: Naresh Aggarwal (Aggarwal and Associates Ltd, Brampton, Canada), Francois Boucher (CHU de Québec - Université Laval, Québec, Canada), Sau-Man Chan (The University of Hong Kong, Hong Kong), Kate Ching-Ching Chan (Department of Paediatrics, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong), Nan-Chang Chiu (Mackay Memorial Hospital, Taipei, Taiwan), Gilbert T Chua (The University of Hong Kong, Hong Kong), Meltem Dinleyici (Eskisehir Osmangazi University, Eskisehir, Turkey), Joseph Domachowske (University Heath Care Center UHCC, Syracuse, Unites States), Ronke Dosunmu (Foundation Pediatrics, East Orange, United States), Peter Dzongowski (Milestone Research, London, Canada), Murdo Ferguson (Colchester Research Group, Truro, Canada), Nicole George (Pediatric Associates of Fairfield, Fairfield, United States), Hsin-Chun Huang (Kaohsiung Chang Gung Memorial Hospital, Kaohsiung City, Taiwan), Tolga Ince (Dokuz Eylul University Medical Faculty, Izmir, Turkey), James Kellner (Alberta Children's Hospital, Calgary, Canada), Daniel Leung (The University of Hong Kong, Hong Kong), Noelle Anne Ngai (Department of Paediatrics, Prince of Wales Hospital, Hong Kong), Sahra Niazi (Midwest Children's Health Research Institute, Lincoln, United States), Christopher Peltier (Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, United States), Christine Rivers (The Corvallis Clinic, Corvallis, United States), Walter Rok (Pediatric Associates of Fall River, Fall River, United States), Stephen Russell (Midwest Childrens Health Research Institute, Lincoln , United States), Gary Schlichter (Murray

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Data sharing statement

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.02.065.

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