Reactogenicity and safety of a liquid human rotavirus vaccine (RIX4414) in healthy adults, children and infants in China
Randomized, double-blind, placebo-controlled phase I studies

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Abbreviations: AE, adverse event; ATP, according to protocol; $CCID_{50}$, median cell culture infective dose; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; GE, gastroenteritis; GMC, geometric mean concentration; RV, rotavirus; RVGE, rotavirus gastroenteritis; SAE, serious adverse event; SBIR, internet-based randomization system; SD, standard deviation; TVC, total vaccinated cohort; WHO, World Health Organization

We report the findings of three randomized, double-blind, placebo-controlled Phase I studies undertaken to support licensure of the liquid formulation of the human G1P[8] rotavirus (RV) vaccine (RIX4414; GlaxoSmithKline Biologicals SA) in China. Healthy adults aged 18–45 y (n = 48) and children aged 2–6 y (n = 50) received a single dose of the human RV vaccine or placebo. Healthy infants (n = 50) aged 6–16 weeks at the time of first vaccination received two oral doses of the human RV vaccine or placebo according to a 0, 1 mo schedule. In infants, blood samples were collected prior to vaccination and one month post-dose 2 to assess anti-RV IgA antibody concentrations using ELISA. Stool samples were collected from all infants on the day of each vaccination, at 7 and 15 d after each vaccination and one month post-dose 2. Stool samples were analyzed by ELISA for detection of RV antigen to assess RV antigen excretion. The reactogenicity profile of the human RV vaccine was found to be comparable to that of placebo in all age groups studied. The anti-RV IgA antibody seroconversion rate in infants after two vaccine doses was 86.7% (95% CI: 59.5–98.3). Vaccine take in infants who received the liquid human RV vaccine was 86.7% (95% CI: 59.5–98.3). A Phase III efficacy study of the human RV vaccine in the infant population in China has now been completed (ROTA-075/NCT01171963).

Rotavirus (RV) is the most common cause of severe gastroenteritis (GE) among infants and young children worldwide. In China, approximately 27000 RV-associated deaths occur among children aged < 5 y annually, with up to 50% of GE hospitalizations in this age group reported to be due to RV infection.[1-4] The annual societal costs of RVGE in China are reported to be approximately US$365 million.[5] The World Health Organization (WHO) recommends inclusion of RV vaccination of infants into all national immunization programs.[6] Modeling estimates suggest that a national RV vaccination program would be a cost-effective measure to reduce deaths, hospitalizations and outpatient visits associated with RV infection in China.[7]

The human G1P[8] RV vaccine (RIX4414; GlaxoSmithKline Biologicals SA) has been shown to be highly efficacious for the prevention of RVGE and associated hospitalizations in large-scale clinical trials worldwide.[8-12] Clinical trial findings have been confirmed in real-life settings after introduction of mass immunization programs. For example, considerable reductions in hospital admissions and mortality due to RVGE and diarrhea of any cause have been observed in infants and young children following inclusion of this vaccine into national childhood immunization schedules in Latin America.[13-22] The human RV vaccine is available as a lyophilized formulation, which is currently registered in more than 110 countries worldwide, and a liquid formulation, which is registered in at least 77 countries. The liquid vaccine formulation has several advantages over the lyophilized formulation, including ease of administration, reduced storage requirements and improved output capacity.

We report results of three Phase I studies undertaken to support licensure of the liquid formulation of the human RV vaccine in China. Adhering to the requirements of the Chinese regulatory authorities, reactogenicity and safety were first assessed in healthy adults aged 18–45 y (ROTA-072/NCT01162590) and children aged 2–6 y (ROTA-073/NCT01086436) prior to initiating a study in the target infant population (ROTA-074/NCT01171963). Infants were required to be aged 6–16 weeks at the time of first vaccination. All studies were conducted according to Good Clinical Practice and in accordance with the Declaration of Helsinki. Study protocols were approved by all relevant institutional review boards. Written informed consent was obtained from subjects or their parents/legal representatives prior to study entry.

In all studies, subjects were required to be of Chinese origin, in good health and free of obvious health problems. Eligible female adult subjects were required to be of non-childbearing potential or to have had a negative pregnancy test on the day of vaccination and to be practicing adequate contraception. Infants with a confirmed history of RVGE were excluded from study participation. Other standard exclusion criteria were applied, as detailed in the ClinicalTrials.gov registry. Children and infants were allowed to receive routine childhood vaccinations according to local immunization practice during the study period, with a minimum interval of at least 7 d between the administration of routine vaccines and the study vaccine or placebo.

All studies were of randomized, double-blind, placebo-controlled design. In each study, subjects were randomly assigned in a 1:1 ratio to receive either the liquid human RV vaccine or placebo. Treatment allocation at the investigator site was performed using an internet-based randomization system (SBIR). Adults and children received a single oral dose of the human RV vaccine or placebo. Infants received two oral doses of the human RV vaccine or placebo according to a 0, 1-mo schedule. Each 1.5 ml dose of the liquid human RV vaccine contained at least $10^{6.0}$ median cell culture infective dose ($CCID_{50}$) of the live attenuated RIX4414 human RV strain.

Diary cards were provided to subjects or their parents/guardians to record solicited adverse events (AE) for 8 d after each vaccination (day 0–7). In adults, solicited AEs were nausea, diarrhea, vomiting, fever, and abdominal pain. In children and infants, solicited AEs were fever, irritability/fussiness, diarrhea, vomiting, loss of appetite and cough/runny nose. The presence and intensity of fever was assessed using two grading scales: one recommended by the Chinese regulatory authorities and another routinely used by GSK Biologicals in studies of the human RV vaccine based on WHO guidelines.[23] Fever was defined as axillary temperature ≥ 37.1°C (according to the grading scales recommended by the Chinese authorities) or ≥ 37.5 °C (according to WHO guidelines).[23] Severity of solicited AEs was graded on a scale from 0 (absent) to 3 (severe), according to pre-specified criteria. Unsolicited AEs were recorded for 31 d after each vaccination (day 0–30). Serious adverse events (SAEs) were recorded for the duration of each study.

In infants, blood samples were collected prior to vaccination and one month post-dose 2 for measurement of anti-RV IgA antibody concentrations using an established in-house enzyme-linked immunosorbent assay (ELISA). The assay cut-off was 20 U/ml. Stool samples were also collected from all infants on the day of each vaccination, at 7 and 15 d after each vaccine dose and one month post-dose 2. Stool samples were analyzed by ELISA for detection of RV antigen to assess RV antigen excretion. Presence of RV antigen demonstrated by ELISA in stool samples from infants who received the human RV vaccine was considered as vaccine virus shedding.

Each study planned to enroll a total of 50 subjects (25 in each group). This target sample size was in accordance with Chinese regulatory guidelines to detect any increase in the incidence of each solicited AE in the vaccine group compared with placebo. Analysis of safety and reactogenicity was performed on the total vaccinated cohort (TVC). The percentage of subjects reporting each individual solicited AE in each group during the 8-d follow-up period was tabulated with exact 95% confidence intervals (CI). The percentage of subjects reporting unsolicited AEs and SAEs was also calculated with 95% CI. In the infant study, immunogenicity was assessed in the according-to-protocol (ATP) population. Geometric mean concentrations (GMC) of anti-RV IgA antibodies were calculated prior to vaccination and one month post-dose 2 with exact 95% CI. The anti-RV IgA antibody seroconversion rate was calculated one month post-dose 2 with exact 95% CI. The percentage of subjects with presence of RV antigen in stool samples was calculated for all pre-determined time-points. Appearance of serum IgA to RV in post-vaccination sera at a concentration of ≥ 20 U/ml in subjects who were negative for RV before the first vaccine dose and/or vaccine virus shedding in any stool sample collected post-vaccination was defined as vaccine take. All statistical analyses were performed using StatXact procedure on SAS®.

The study in adults was conducted from March 1–31, 2010. A total of 52 adults were enrolled. Four adults were excluded from the total vaccinated cohort (2 subjects did not receive the study vaccine and 1 subject from each group was eliminated after vaccination due to lack of pregnancy testing). The total vaccinated cohort for the adult study therefore consisted of 48 subjects (25 in the vaccine group and 23 in the placebo group). Mean age of adults at the time of vaccine administration was 32.3 y (range, 20–44 y) and 45.8% of all subjects were male. No solicited AEs were reported in either group during the 8-d follow-up period after vaccination. Unsolicited AEs were reported by only one adult in each group (one adult reported headache and oropharyngeal pain in the vaccine group and one adult reported periodontitis in the placebo group, which were considered unrelated to vaccination). No SAEs were reported in either group during the study period.

The study in children was conducted from March 13–April 16, 2010. A total of 50 children were enrolled and vaccinated (25 in each group). Mean age at the time of vaccination was 3.8 y (range, 2–5 y) and 50.0% were male. During the 8-d follow-up period after vaccination, at least one solicited or unsolicited AE was reported for 14 children in the vaccine group [56.0% (95% CI: 34.9–75.6)] and 13 children in the placebo group [52.0% (95% CI: 31.3–72.2)]. Cough was the most frequently reported

solicited AE, reported for 10 children in the vaccine group [40.0% (95% CI: 21.1–61.3)] and 12 children in the placebo group [48.0% (95% CI: 27.8–68.7)] (**Table S1**). No solicited AEs of grade 3 severity were reported during the 8-d follow-up period in the vaccine group. In the placebo group, grade 3 diarrhea was reported in one child. Unsolicited AEs were reported during the 31-d post-vaccination period for 11 children in the vaccine group [44.0% (95% CI: 24.4–65.1)] and 13 children in the placebo group [52.0% (95% CI: 31.3–72.2)]. The most common unsolicited AEs during the 31-d post-vaccination period were cough (reported for 3 and 5 children in the two groups, respectively) and nasopharyngitis (reported for 3 and 4 children, respectively). No unsolicited AEs of grade 3 severity or SAEs were reported in either group during the study period.

The study in infants was conducted from 13 April–28 June 2010. A total of 50 infants were enrolled and vaccinated (25 in each group). Mean age was 11.0 weeks (range, 6–16 weeks) at dose 1 and 15.8 weeks (range, 11–20 weeks) at dose 2, and 54.0% of enrolled infants were male. Demographic characteristics at baseline were similar in the two groups (**Table 1**). All infants received at least one dose of study vaccine or placebo and were included in the TVC for analysis of reactogenicity and safety. Most infants (90%) received both doses of vaccine or placebo (23 in the vaccine group and 22 in the placebo group).

During the 8-d follow-up period after vaccination, at least one solicited or unsolicited AE was reported for 9 infants in the vaccine group [36% (95% CI: 18.0–57.5)] and 13 infants in the placebo group [52% (95% CI: 31.3–72.2)]. Solicited AEs of grade 3 intensity were reported by 3 infants [12% (95% CI: 2.5–31.2)] in the vaccine group and 1 infant [4% (95% CI: 0.1–20.4)] in the placebo group during the 8-d follow-up period. **Table 2** shows the overall incidence of each solicited AE during the 8-d follow-up period after either vaccine dose. Post-dose 1, irritability was the most frequently reported solicited AE, occurring in 5 infants in the vaccine group [20.0% (95% CI: 6.8–40.7)] and 6 infants in the placebo group [24.0% (95% CI: 9.4–45.1)]. Post-dose 2, the most frequently reported solicited AEs were fever (according to the Chinese scale), which was reported for 3 infants in the vaccine group [13.0% (95% CI: 2.8–33.6)] and 6 infants in the placebo group [27.3% (95% CI: 10.7–50.2)], and diarrhea, which was reported for 4 infants in each group [17.4% (95% CI: 5.0–38.8)] and [18.2% (95% CI: 5.2–40.3)] in the two groups, respectively.

At least one unsolicited AE was reported for 6 infants in the vaccine group and 3 infants in the placebo group during the 31-d follow-up period after either vaccine dose. Nasopharyngitis was the most frequently reported unsolicited AE in both groups (reported for 4 and 3 infants in the two groups, respectively). One infant in the vaccine group reported two SAEs (bronchopneumonia and congenital heart disease reported 2 d post-dose 1). Neither of these SAEs was considered related to study vaccine administration. No cases of intussusception were reported in either group during the study period. No infant was withdrawn from the study due to AEs.

A total of 32 infants were included in the ATP cohort for analysis of immunogenicity (15 in the vaccine group and 17 in the

Table 1. Demographic characteristics for infants receiving at least one dose of the human RV vaccine or placebo in ROTA-074 (ROTA-074 infant study; TVC)

Characteristic	Human RV vaccine (n = 25)	Placebo (n = 25)
Age at dose 1, weeks		
Mean (SD)	10.3 (2.70)	11.8 (2.43)
Median (range)	10 (6–16)	13 (7–15)
Age at dose 2, weeks		
Mean (SD)	15.2 (2.71)	16.4 (2.38)
Median (range)	15 (11–20)	17 (11–20)
Gender, n (%)		
Female	13 (52.0)	10 (40.0)
Male	12 (48.0)	15 (60.0)
Ethnicity, n (%)		
East Asian	25 (100)	25 (100)

SD, standard deviation.

Table 2. Percentage of subjects reporting each solicited AE during the 8-d follow-up period (day 0–7) after either vaccine dose (all and grade 3 intensity) (ROTA-074 infant study; TVC)

	Human RV vaccine (n = 25)		Placebo (n = 25)	
	n (%)	95% CI	n (%)	95% CI
Cough	6 (24)	9.4, 45.1	8 (32)	14.9, 53.5
All				
Grade 3	0 (0)	0.0, 13.7	0 (0)	0.0, 13.7
Diarrhea	7 (28)	12.1, 49.4	5 (20)	6.8, 40.7
All				
Grade 3	3 (12)	2.5, 31.2	1 (4)	0.1, 20.4
Irritability	5 (20)	6.8, 40.7	7 (28)	12.1, 49.4
All				
Grade 3	0 (0)	0.0, 13.7	0 (0)	0.0, 13.7
Loss of appetite	5 (20)	6.8, 40.7	7 (28)	12.1, 49.4
All				
Grade 3	0 (0)	0.0, 13.7	0 (0)	0.0, 13.7
Fever (WHO scale)	1 (4)	0.1, 20.4	3 (12)	2.5, 31.2
All (≥ 37.5°C)				
Grade 3 (≥ 39.0°C)	0 (0)	0.0, 13.7	0 (0)	0.0, 13.7
Fever (Chinese scale)	3 (12)	2.5, 31.2	7 (28)	12.1, 49.4
All (≥ 37.1°C)				
Grade 3 (≥ 39.0°C)	0 (0)	0.0, 13.7	0 (0)	0.0, 13.7
Vomiting	2 (8)	1.0, 26.0	2 (8)	1.0, 26.0
All				
Grade 3	1 (4)	0.1, 20.4	0 (0)	0.0, 13.7

Grade 3 AEs defined as cough which prevented normal daily activity, ≥ 6 looser than normal stools per day, crying that could not be comforted or which prevented normal daily activity, not eating at all, and ≥ 3 episodes of vomiting/day. 95% CI, 95% confidence interval.

placebo group). Reasons for exclusion from the ATP cohort were study vaccine not administered according to protocol (2 subjects in each group), initially seropositive or unknown RV IgA status (3 and 2 subjects, respectively) and essential serological data missing (5 and 4 subjects, respectively). One month post-dose 2, the anti-RV IgA antibody seroconversion rate was 86.7% (95% CI: 59.5–98.3) in the vaccine group. No subjects in the placebo group seroconverted during the study period. In seropositive subjects in the vaccine group, anti-RV IgA antibody GMC one month after administration of the second vaccine dose was 453.7 U/ml (95% CI: 204.1–1008.4). RV antigen in stool samples collected at pre-determined time-points was only detected in 2 subjects in the vaccine group 7 d post-dose 1 and in 1 subject in the placebo group one month post-dose 2. Vaccine take in infants who received the liquid human RV vaccine was 86.7% (95% CI: 59.5–98.3).

Results of these preliminary studies in China confirm that the liquid human RV vaccine has acceptable safety and reactogenicity. All studies were of randomized, double-blind design to ensure unbiased reactogenicity and safety evaluation. The reactogenicity profile of the vaccine was comparable to that of placebo in all age groups studied. This is in keeping with the results of previous studies of the human RV vaccine conducted in other Asian countries, including Singapore, Hong Kong, Taiwan, Vietnam, Philippines and Korea.[10,24,25] The seroconversion rate of 86.7% observed in infants after two vaccine doses in this study is similar to that reported in Korean infants in a recent post-licensure study [88.1% (95% CI: 84.0–91.4).][25] Evaluation of the efficacy of the human RV vaccine in infants was not within the scope of these preliminary Phase I studies. A Phase III efficacy study of the liquid human RV vaccine in the infant population in China has now been completed (ROTA-075/NCT01171963).

Supplemental Material

Supplemental materials may be found here:
www.landesbioscience.com/journals/vaccines/article/25076

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