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Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No1901/2006, as amended

Rotarix

rotavirus vaccine, live

Procedure No: EMEA/H/C/000639

P46 059

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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The study is a placebo-controlled randomized controlled trial on the efficacy of the rotavirus vaccine.

The **primary objective** of the study is to determine if two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine can prevent any RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.

Secondary objectives include:

Efficacy

• To assess the efficacy of two doses of the lyophilized formulation of GSK Biologicals' HRV vaccine against severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the efficacy follow-up period.

• To assess the efficacy of two doses of the lyophilized formulation of GSK Biologicals' HRV vaccine against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains of G1 serotype during the efficacy follow-up period.

• To assess the efficacy of two doses of the lyophilized formulation of GSK Biologicals' HRV vaccine against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains of non-G1 serotypes during the efficacy follow-up period.

• To assess the efficacy of two doses of the lyophilized formulation of GSK Biologicals' HRV vaccine against hospitalisation due to RV GE caused by the circulating wild-type RV strains during the efficacy follow-up period.

• To assess vaccine efficacy against any RV GE and severe RV GE leading to a medical intervention and caused by the circulating wild-type RV strains during the period starting from Dose 1 up to Visit 5.

Safety and reactogenicity

• To assess the reactogenicity of two doses of the lyophilised formulation of GSK Biologicals' HRV vaccine compared with placebo in terms of solicited symptoms.

• To assess the safety of two doses of the lyophilized formulation of GSK Biologicals' HRV vaccine compared with placebo in terms of unsolicited adverse events (AEs) (31 days after each dose) and serious adverse events (SAEs) during the entire course of the study.

Immunogenicity [in the immunogenicity subset (N = 60)]

• To explore the immunogenicity of GSK Biologicals' HRV vaccine in terms of serum anti-rotavirus IgA antibody concentrations one month after the second study vaccine dose.

Quality appraisal of the study

1. The study addresses an appropriate and clearly focused question.

2. The assignment of subjects to treatment groups was randomized, in a 2:1 ratio.

3. An adequate concealment method was used, with an internet based randomization scheme using a computer generated list.

4. Subjects and investigators were kept blind about treatment allocation. However, there is no mention of whether the treating physicians were kept blind (risk for contamination?).

5. The treatment and control groups appear similar at the start of the trial for age, gender, race, height and weight; although no formal statistical testing was performed. Other important variables, such as the presence of siblings, are not reported.
   It is unclear whether the only difference between groups is the treatment under investigation, as there is very limited information on concomitant treatments except concomitant and intermittent vaccinations, and there is uncertainty on the blinding of the treating physicians. In addition, subjects taking a drug or vaccine other than the study vaccine were included in the total vaccinated cohort analysis, but were removed from the according to protocol analyses. However, table 13 makes no mention of such removals, making it very unlikely all other drugs were recorded.

6. Have all relevant outcomes been measured in a standard, valid and reliable way? The primary outcome was measured by active follow-up for occurrence of GE leading to medical intervention by contact of study personnel with each subject's parent/guardian every two weeks. For each GE episode leading to medical intervention occurring during the study period, a GE diary card was completed by the parents/guardians daily until end of the GE symptoms. Information on all medical attention obtained related to this GE leading to medical intervention was recorded on the same card. The completed diary cards were returned to the investigator at the following study visit. Medical attention (medical doctor visit, emergency room visit or hospitalisation) was also recorded for each GE episode.
   The information collected on the GE diary card allowed the assessment of the intensity of each GE episode using the Vesikari scale, a 20-point scoring system. Points were assigned at GSK Biologicals according to duration and intensity of diarrhoea and vomiting, the intensity of fever, use of rehydration therapy or hospitalisation for each episode of GE. Based on a table detailing how this scale was used, it is unclear how a score of <7 can be obtained, as the scale consists of 7 items and the minimum score is 1 (and for dehydration the minimum score is 2). A total score of <7 can only be possible if 0 is assigned to items in case they are absent.

   Stool samples were collected for each GE episode leading to medical intervention. Samples were then tested at GSK Biologicals using Enzyme Linked immunosorbent assay (ELISA) to detect RV. If positive, the sample was tested by polymerase chain reaction (PCR) to determine the G and the P genotypes. If any G1 RV was detected, vaccine virus was differentiated from the wild type serotype by Reverse Transcriptase Polymerase Chain Reactions (RT-PCR) followed by reverse hybridisation assay or an equivalent approach.

   For the secondary objectives, serum obtained from whole blood samples collected from subjects in the immunogenicity subset at Visit 1 and Visit 3 were tested by ELISA at GSK Biologicals' central laboratory to measure serum anti-rotavirus IgA antibody concentrations. The assay cut-off was 20 U/mL. Adverse events were solicited by asking the following question: "Has your child acted differently or felt different in any way since receiving the vaccine or since the last visit?". Adverse events were then followed-up and assessed for intensity, causality and outcome.

   Although the measurement of the outcomes is standardized, it is surprising to find a difference in the proportion of stool samples that were analysed for RV between the vaccine group and the placebo group: stool analysis results were not available for 23 (7.3%) GE episodes in the HRV group and for 6 (3.5%) GE episodes in the placebo group because stool samples were either not tested or not collected.

7. What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?
   17/508 withdrawals in vaccine group, 11/257 withdrawals in placebo group

8. All the subjects are analyzed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)
   Analyses are carried out on an according to protocol (ATP) and on the total vaccinated cohort. The latter does not constitute a true intention to treat analysis as it only comprises all subjects enrolled and vaccinated (and not those enrolled either vaccinated or not).

The ATP cohort for efficacy included all subjects:

• who received two doses of HRV vaccine or placebo,

• who entered the efficacy surveillance period:
– had follow-up beyond 2 weeks after Dose 2 of study vaccination,

• who had no rotavirus other than vaccine strain in GE stool samples collected between the day of Dose 1 and 2 weeks after Dose 2 of HRV vaccine or placebo,

• for whom the randomisation code was not broken,

• who did not receive a vaccine forbidden by or not specified in the protocol.

ATP cohort for safety

The ATP cohort for safety included all vaccinated subjects:

• who received at least one dose of HRV vaccine or placebo,

• for whom the randomisation code was not broken,

• who did not receive a vaccine forbidden by or not specified in the protocol.

Elimination criteria: these children were excluded from the according-to-protocol analyses:

• Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine during the study period.

• Chronic administration (defined as more than 14 days) of immunosuppressants during the study period (Inhaled and topical steroids were allowed).

• Administration of immunoglobulin and/or any blood products during the study period.

• Any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination (no laboratory testing was required).

9. Where the study is carried out at more than one site, results are comparable for all sites: no information available.

In conclusion, this is a RCT with adequate concealment of allocation and blinding of patients and assessors. However, there is an unexplained difference in the proportion of stool samples analysed for rotavirus. This difference leads to an increase of the efficacy of the vaccine, thus resulting in biased results.

Results

TOTAL VACCINATED COHORT

During the period from Dose 1 up to the data lock point, a total of 207 subjects (40.7%) in the vaccine group and 108 subjects (42.0%) in the placebo group reported any GE.

Any RV GE caused by wild-type RV leading to medical intervention occurred in 1.8% in the vaccine group compared to 10.1% in the placebo group (p-value <0.001). Vaccine efficacy against any RV GE caused by wild-type RV leading to medical intervention was 82.5% [95% CI: 61.4%; 92.8%].

Severe GE was recorded in 9.4% of subjects in the vaccine group compared to 12.5% in the placebo group (no p-value provided).

Severe RV GE caused by wild-type RV leading to medical intervention occurred in 0.2% in the HRV group compared to 4.7% in the placebo group (p-value <0.001). Vaccine efficacy against severe RV GE caused by wild-type RV leading to medical intervention was 95.8% [95% CI: 71.5%: 99.9%].

Only 1 hospitalisation due to RV GE in each group was recorded in this first data-analysis (study still ongoing).

ACCORDING TO PROTOCOL ANALYSES

A total of 191 subjects (38.4%) from the HRV group and 100 subjects (40.0%) from the placebo group had report of at least one GE episode leading to medical intervention.

Of all the GE episodes leading to medical intervention that were tested, rotavirus was detected in 9 GE episodes (1.8%) in the HRV group and 25 GE episodes (10.0%) in the placebo group.

Significantly fewer subjects in the HRV group reported severe RV GE leading to medical intervention caused by circulating wild-type RV compared to the placebo group (0.2% versus 4.4%, p-value <0.001). Vaccine efficacy against severe RV GE leading to medical intervention caused by circulating wild-type RV was 95.4% [95% CI: 68.6%; 99.9%].

When the GE and RV GE episodes leading to medical intervention were scored using the 20-point Vesikari scale, the distribution of reported GE episodes leading to medical intervention among mild, moderate and severe intensity was similar in both groups but there were more cases rated as severe (≥11 points) in terms of RV GE episodes in the placebo group (11 RV GE episodes [44.0%]) as compared to the HRV group (1 RV GE episode [11.1%])

Adverse events (based on Total Vaccinated cohort)

During the entire study period, majority of the SAEs were classified under SOC MedDRA PT for “Bronchitis” (14 subjects in the HRV group and none in the placebo group), “Pneumonia” (12 subjects in the HRV group and 4 subjects in the placebo group) and “Gastroenteritis” (11 subjects in the HRV group and 2 subjects in the placebo group).

Conclusion:

The study itself is relatively small, with some methodological problems mainly the difference in the proportion of verification of stool samples between the vaccine group and the placebo group and the uncertainty on whether the two groups had any concomitant drugs (such as anti-emetics, stool cosmetics, etc).
The trial is ongoing and the current results are to be considered preliminary. Only one hospitalization for RV GE occurred in each group.