18 November 2014
EMA/73981/2010
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report under Article 46

## RotaTeq

International non-proprietary name: Live attenuated rotavirus vaccine

Procedure No: EMEA-H-C-669-P46-029

### Note

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

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# 1. INTRODUCTION

On 9th December 2009 the MAH submitted the study report on P021 in accordance with Article 46 of the Regulation (EC) No 1901/2006, as amended, on medicinal products for paediatric use.

A clinical study report plus a short critical expert overview were provided.

The MAH stated that the submitted paediatric study does not influence the benefit-risk relationship for RotaTeq and there is no consequential regulatory action.

The CHMP agrees that the MAH has fulfilled Article 46 as a result of this submission and that there are no implications for the prescribing information.

# 2. SCIENTIFIC DISCUSSION

### Introduction

The MAH submitted a CSR for study P021, which was conducted in India during 2008 to support the licensing of the vaccine in that country.

### Clinical studies

#### P021

The study evaluated the safety, tolerability and immunogenicity of RotaTeq in 110 healthy 6- to 12-week old Indian infants. All subjects were to receive 3 doses (4 to 10 weeks apart) of RotaTeq orally. RotaTeq was co-administered with approved routine vaccines for infants, including oral polio vaccine, inactivated polio vaccine, diphtheria, tetanus and pertussis vaccine, *Haemophilus influenzae* type b vaccine, pneumococcal conjugate vaccine and hepatitis B vaccine.

Blood samples were obtained for evaluation of serum anti-rotavirus IgA and serum neutralising antibodies (SNA) against rotavirus serotypes G1, G2, G3, G4, and P1 prior to the first dose and 14 days after the last dose. Samples were shipped to the MAH's usual testing facilities for IgA and SNA serological responses.

There were 110 subjects enrolled (14-40 at each site) and all received at least one dose of RotaTeq in this study starting from May 2008 to August 2008 at four study sites. Of the 110, 103 received all three doses and 102 attended the D14 visit. Three of these 102 subjects had major protocol deviations (in each case too short an interval between doses) and were excluded from the per-protocol population for the immunogenicity analysis.

As shown below, there were slightly more males and females and the mean age at enrolment was about 8.5 weeks. Most children had no significant medical history and only one had been born prematurely.

The majority of children had at least one concomitant vaccination at each study visit (62% at visit 1, 81% visit 2 and 64% visit 3).

| Variable | Statistics / Category | Baseline Value |
|---|---|---|
| Gender | Male | 63 (57.27 %) |
| | Female | 47 (42.73 %) |
| Age (In Days) | N | 110 |
| | Mean | 59.01 |
| | Std Dev | 13.52 |
| | Median | 54.00 |
| | (Min, Max) | (42.00 , 88.00) |
| Height (cms) | N | 110 |
| | Mean | 57.61 |
| | Std Dev | 5.04 |
| | Median | 57.00 |
| | (Min, Max) | (50.00 , 98.00) |
| Weight (kg) | N | 110 |
| | Mean | 4.73 |

In the PP population of 99 subjects there was a ≥3-fold increase in SNA for serotypes G1, G2, G3, G4, and P1A[8] in varying percentages of subjects, ranging from 14% for G2 up to 38% for G1. Results were very similar for the FAS. However, the baseline GMTs ranged from 28 for G3 to 84 for P1. Also, the GMTs showed no appreciable rise for G3 and decreased for G2 from baseline to post-dose 3.

**≥ 3-fold rise responses in SNA**

| Rotavirus Serotype | N | M | Percentage | 95 % C.I |
|---|---|---|---|---|
| G1 | 99 | 37 | 37.37 | (27.84 , 46.90) |
| G2 | 99 | 14 | 14.14 | (7.28 , 21.00) |
| G3 | 99 | 29 | 29.29 | (20.33 , 38.25) |
| G4 | 99 | 35 | 35.35 | (25.93 , 44.77) |
| P1A[8] | 99 | 29 | 29.29 | (20.33 , 38.25) |

**SNA GMTs to Rotavirus Serotypes G1, G2, G3, G4 and P1A[8]**

| Rotavirus Serotype | | PP Population ( N = 99) | |
|---|---|---|---|
| | | GMTs | 95% C.I. |
| G1 | Pre dose 1 | 43.11 | (35.07 , 52.98) |
| | Post dose 3 | 81.19 | (65.15 , 101.19) |
| G2 | Pre dose 1 | 62.91 | (52.91 , 74.79) |
| | Post dose 3 | 49.21 | (40.62 , 59.61) |
| G3 | Pre dose 1 | 27.71 | (21.48 , 35.73) |
| | Post dose 3 | 32.95 | (25.60 , 42.41) |
| G4 | Pre dose 1 | 51.74 | (42.94 , 62.35) |
| | Post dose 3 | 80.88 | (66.52 , 98.34) |
| P1A[8] | Pre dose 1 | 84.17 | (67.27 , 105.31) |
| | Post dose 3 | 100.01 | (79.28 , 126.15) |

Among 99 in the per-protocol population 82 (82.83%; [CI: 75.40, 90.26]) exhibited a ≥3-fold rise from pre-dose 1 to post-dose 3 in serum anti-rotavirus IgA. The IgA GMT increased from 3.7 at baseline to 75 after the third dose. In the FAS 84/102 (82%) had a ≥3-fold rise and the GMT increased from 3.8 to 80.

| Antibodies | N | M | Percentage | 95 % C.I |
|---|---|---|---|---|
| Serum anti-rotavirus IgA | 99 | 82 | 82.83 | (75.40 , 90.26) |
| Note: N-Number in PP Set<br>M-Number of subjects who attained threefold increase | | | | |

**GMTs of Serum Anti-Rotavirus IgA**

| Rotavirus Serotype | | PP Population ( N = 99) | |
|---|---|---|---|
| | | GMTs | 95% C.I. |
| Serum anti-rotavirus IgA | Pre dose 1 | 3.68 | (2.66, 5.09) |
| | Post dose 3 | 75.12 | (51.67, 109.22) |

The table on the next page shows data from three prior studies reported by the MAH for comparison.

**Anti-Rotavirus IgA and SNA to Rotavirus Serotypes G1, G2, G3, G4 and P1A[8] in prior studies**

| Serotype and Parameters | | P006† | | P007 | | P009‡ | |
|---|---|---|---|---|---|---|---|
| | | n | Result (95% CI) | n | Result (95% CI) | n | Result (95% CI) |
| **G1** | GMT and 95% CI | 218 | 239.8 (201.8, 285.0) | 68 | 124.3 (83.6, 185.0) | 551 | 177.4 (157.7, 199.6) |
| | 3-Fold Rise and 95% CI | 207 | 76.0 (69.6, 81.6) | 67 | 56.7 (44.0, 68.8) | 66 | 42.4 (30.3, 55.2) |
| **G2** | GMT and 95% CI | 218 | 26.9 (22.8, 31.6) | 68 | 10.4 (8.1, 13.3) | 551 | 20.4 (18.5, 22.5) |
| | 3-Fold Rise and 95% CI | 207 | 34.3 (27.9, 41.2) | 62 | 14.5 (6.9, 25.8) | 66 | 37.9 (26.2, 50.7) |
| **G3** | GMT and 95% CI | 222 | 16.7 (14.3, 19.5) | 68 | 9.8 (7.7, 12.6) | 551 | 17.0 (15.5, 18.8) |
| | 3-Fold Rise and 95% CI | 213 | 22.1 (16.7, 28.2) | 67 | 9.0 (3.4, 18.5) | 66 | 18.2 (9.8, 29.6) |
| **G4** | GMT and 95% CI | 218 | 72.6 (61.3, 85.9) | 68 | 47.2 (34.7, 64.4) | 551 | 68.7 (63.0, 75.0) |
| | 3-Fold Rise and 95% CI | 207 | 54.1 (47.1, 61.0) | 63 | 39.7 (27.6, 52.8) | 66 | 63.6 (50.9, 75.1) |
| **P1A[8** | GMT and 95% CI | 214 | 112.6 (94.3, 134.5) | 67 | 27.9 (20.2, 38.5) | 551 | 69.8 (63.3, 76.9) |
| | 3-Fold Rise and 95% CI | 203 | 53.7 (46.6, 60.7) | 61 | 24.6 (14.5, 37.3) | 66 | 39.4 (27.6, 52.2) |
| **IgA** | GMT and 95% CI | 197 | 337.6 (265.6, 429.3) | 68 | 200.0 (131.9, 303.0) | 554 | 277.1 (248.8, 308.6) |
| | 3-Fold Rise and 95% CI | 189 | 95.2 (91.2, 97.8) | 67 | 95.5 (87.5, 99.1 ) | NA | NA |

† Subjects with scheduled 14 days post-dose 3 serum samples in the per-protocol population.

‡ Data shown for combined lots.

GMT = Geometric mean titer

CI = Confidence interval

Safety data were collected (including with use of 7-day diary cards) during the 14-day period after each dose. There were 104 subjects who had follow-up data and were included in the safety analyses of which 47 (45.2%) had at least one AE with a total of 96 AEs reported. The incidence of AEs decreased with subsequent study vaccine doses (from 57 post dose-1, 20 post dose-2 and 19 post dose-3. Overall 17/96 AEs were deemed related to the study vaccine by the investigators.

| Description | Statistics |
|---|---|
| Proportion of Subjects who experienced at least one adverse event | 47 (45.19 %) |
| Proportion of Subjects who experienced at least one adverse events at Visit 2 | 33 (31.73%) |
| Proportion of Subjects who experienced at least one adverse events at Visit 3 | 17 (16.50 %) |
| Proportion of Subjects who experienced at least one adverse events at Visit 4 | 9 (8.74 %) |
| *Percentages are calculated keeping 'number of subjects attending that particular visit' in denominator | |

The most frequent adverse experience was diarrhoea (30/96 AEs), followed by 29 reports of vomiting and 19 of pyrexia. The reporting rates were within the range observed in the Phase III clinical studies.

**Specific AEs within 14 days Post-vaccination with any dose**

| | RotaTeq | |
|---|---|---|
| | n | % |
| **Diarrhoea** | 22 | 21.2% |
| **Pyrexia** | 14 | 13.5% |
| **Irritability** | 1 | 1% |
| **Vomiting** | 20 | 19.2% |
| Calculation of percentage:<br>The number of subjects with an adverse experience divided by the number of subjects with follow-up (104).<br>Pyrexia was defined as (rectal temperature ≥38.1°C (≥100.5°F); axillary temperature >37.0 °C (>96.8°F) confirmed by rectal measurement)<br>n = Number of vaccinated subjects with adverse experience. | | |

**Specific AEs within 7 days post-vaccination with any dose**

| | RotaTeq | | |
|---|---|---|---|
| | P006 | P007 | P009[†] |
| **Diarrhoea** | 13.9% | 10.3% | 43.4% |
| **Elevated Temperature** | 34.1% | 30.0% | 47.4% |
| **Irritability** | 12.0% | 16.2% | 15.5% |
| **Vomiting** | 9.4% | 8.8% | 30.2% |

There was one SAE of meningitis (SAE), accounting also for the only withdrawal due to an AE. No treatment was given to other AEs and all recovered completely.

**Discussion on clinical aspects**

In India, 1/250 children or about 100,000 – 150,000 children die due to rotavirus diarrhoea each year, accounting for 17% of the world's estimated rotavirus deaths. The susceptible age group is between 6 to 24 months. The most common G and P types reported from India include G1, G2, G4, G9, P[4], P[6], and P1A[8].

The MAH concluded that the magnitude of antibody responses across the clinical studies has been variable but the results of P021 were comparable to responses seen in one or more of the previously reported Phase III clinical studies. Also, that the differences in magnitude of antibody responses have not resulted in differences in protective efficacy. On this basis the MAH concludes that the vaccine will be efficacious in Indian infants.

For SNA responses it can be agreed that the results in these Indian infants overlap in terms of proportions with at least 3-fold rises and in GMTs with data reported from prior studies in non-Indian infants. However, the baseline GMTs were already quite high in the Indian infants, presumably due to maternal antibody, and not all showed an increase in response to vaccination.

For IgA against rotavirus the post-dose 3 GMT in this Indian study was less than half that reported in prior studies and the proportion with at least a 3-fold increase was about 82% compared to about 95% in non-Indian studies.

The safety profile in Indian infants did not seem to be any different from that in non-Indian infants.

Overall it can be agreed that these data have no implications for the EU SmPC. Whether or not RotaTeq will be as effective in India as observed in the US cannot be gauged from these serological data.

# *3.* CHMP OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The submission is satisfactory and Art 46 may be considered fulfilled.

- **Recommendation**

**Fulfilled –** No further action required

# *4.* ADDITIONAL CLARIFICATION REQUESTED

Not applicable