14 June 2012
EMA/251107/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

RotaTeq

rotavirus vaccine, live, oral

Procedure No.: EMEA/H/C/000669/II/0031

Note

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

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LIST OF ABBREVIATIONS

CI	Confidence Interval
ER	Emergency Room
HCRU	Healthcare resource utilisation
IS	Intussusception
PIP	Paediatric Investigation Plan
PP	Per Protocol (population)
RMP	Risk Management Plan
RVGE	Rotavirus gastro-enteritis
SIDS	Sudden Infant Death Syndrome

1. Background information on the procedure

1.1. Requested Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Sanofi Pasteur MSD, SNC submitted to the European Medicines Agency on 11 July 2011 an application for a Type II variation.

This application concerns the following medicinal product:

Medicinal product:	International non-proprietary name:	Presentations:
RotaTeq	rotavirus vaccine, live, oral	See Annex A

The following variation was requested:

Variation requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

To extend the upper limit of the administration of the third dose of vaccine from up to 26 weeks to up to 32 weeks of age.

The requested variation proposed amendments to the SmPC and Package Leaflet.

Rapporteur: Ian Hudson

1.2. Steps taken for the assessment

Submission date:	11 July 2011
Start of procedure:	24 July 2011
Rapporteur's preliminary assessment report circulated on:	27 July 2011
Request for supplementary information and extension of timetable adopted by the CHMP on:	20 October 2011
MAH's responses submitted to the CHMP on:	18 November 2011
Rapporteur's assessment report on the MAH's responses circulated on:	13 December 2011
CHMP opinion:	19 January 2012

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/149/2011) on the agreement of a paediatric investigation plan (PIP)

At the time of submission, the PIP P/149/2011 was completed.

The PDCO issued an opinion on compliance for the PIP P/149/2011.

2. Scientific discussion

2.1. Introduction

RotaTeq is currently indicated in the European Union for the active immunisation of infants from the age of 6 weeks to 26 weeks for prevention of gastroenteritis due to rotavirus infection.

The purpose of this variation is to extend the upper age limit for the administration of the third dose of vaccine from 26 to 32 weeks of age. Making this change has implications for sections 4.1 and 4.2 of the SmPC and the MAH also proposes modifications to sections 4.8 and 5.1. The extended age range has implications also for section 3 of the PL.

In support of this variation the MAH has submitted post-hoc sub-analyses of data from previously completed Phase III studies 006, 007 and 009. The purpose of these analyses was to evaluate the safety and efficacy of RotaTeq in infants who received the third dose of vaccine at age > 26 to ≤ 32 weeks. In addition, the MAH conducted sub-analyses of safety data among infants who received their third dose of RotaTeq when they were aged > 26 weeks to ≤ 32 weeks in the completed post marketing safety surveillance study 019. No newly reported studies are included in this application.

Prior to filing this variation the MAH submitted a Paediatric Investigation Plan (P/149/2011), which has been approved. The measures presented in this application were performed in line with the corresponding PIP Decision (P/149/2011) and a positive opinion on compliance check has been adopted by the PDCO (EMEA-C-000967-PIP01-10).

2.2. Clinical aspects

In the pre-approval clinical studies the third dose of RotaTeq could be administered up to 32 weeks of age although the actual mean age of infants at the time of the last dose was approximately 26 weeks. Since 2006 the vaccine has been used in the United States with a recommended age range of 6 to 32 weeks of age. As of December 2010, over 44 million doses have been distributed worldwide, of which approximately 36 million have been distributed in the U.S.

RotaTeq was initially approved in the EU (June 2006) with an upper age limit of 26 weeks for the third dose, which reflected the mean age in Phase III prelicensure studies. This was considered necessary to avoid administration of the last dose during the age range for peak incidence of naturally-occurring intussusception, which was thought at the time of approval to be approximately 32 weeks of age in Europe. Since initial licensure, new information concerning the natural background incidence of intussusception in Denmark, Switzerland and Germany suggest that the peak occurs or at least begins before 26 weeks of age. This corresponds to the US peak age of naturally-occurring intussusception between approximately 21 to 26 weeks.

The MAH stated in this procedure that the extension of administration of Dose 3 until 32 weeks of age is not expected to lead to additional safety concerns with respect to intussusception and will allow for improved adherence to the 3-dose regimen. For example, the 2-4-6 months primary infant immunisation schedule is currently in use in Spain, Portugal, Ireland, Austria, Romania, Cyprus and Poland and other countries with a vaccination visit at 6 months of age are Bulgaria, Czech Republic, Estonia, Greece, Ireland, Latvia and Slovenia. In reality, the exact timing of administration of the third vaccine doses may be > 26 weeks of age. There is also a possibility that the third dose of RotaTeq would be missed entirely if not administered by 26 weeks of age because of circumstances such as intercurrent illness or scheduling difficulties. The data re-analysed in this application come from three pre- and one post-marketing studies, which have all been submitted and fully assessed previously:

- 006 (REST)
- 007 (Vaccine at Expiry Potency)
- 009 (3 Consistency Lots)

  These were randomised, multicentre, in-house blinded placebo-controlled studies conducted throughout the United States, Europe, Latin America and Asia. Healthy infants aged 6 through 12 weeks were enrolled in the studies. Subjects received 3 oral doses of RotaTeq or placebo administered at intervals of 4 to 10 weeks (28 to 70 days). The last dose was administered by 32 weeks of age.

- 019 - Post-Marketing Evaluation of the Short-Term Safety of RotaTeq

  This was a prospective observational study to monitor the safety profile of RotaTeq in the post-licensure period in a large number of subjects under conditions of routine use. The setting for this study was based on, a proprietary research database built from electronically captured provider, facility and pharmacy claims with large private health plans and large employer groups. The individuals covered by this health plan are geographically diverse across the United States.

Please see previous assessment reports for full details of the study objectives, designs and results for the total study populations.

2.2 Clinical Efficacy aspects

2.2.1. Methods – analysis of data submitted

The primary objective was to evaluate efficacy against any severity of rotavirus gastro-enteritis (RVGE) caused by serotypes G1, G2, G3, and G4 occurring at least 14 days following the third dose in the subset of subjects who were aged > 26 weeks and ≤ 32 weeks upon receipt of the third dose.

The data from 006 and 007 were combined. The combined analysis was based on the per-protocol population comprised of subjects enrolled who received the 3 scheduled doses of RotaTeq or placebo and adhered to the guidelines for administration of vaccine. Thus, all subjects who were not protocol violators and received dose 3 up to 32 weeks of age were included in the analyses.

Efficacy = (1 - relative risk), where relative risk is the incidence in the vaccine group divided by the incidence in the placebo group. An estimate of efficacy and an associated 95% confidence interval were calculated. The confidence interval was based on a binomial distribution for the number of subjects classified as cases in the vaccine group relative to the total number of subjects classified as cases that is formed by conditioning on the total number of subjects classified as cases. The estimate and confidence limits for efficacy were then computed using the relationship efficacy = (1-(k+1)p) / (1-p), where p is the corresponding parameter of interest from the binomial distribution and k is the total amount of follow-up time in the placebo group divided by the total amount of follow-up time in the vaccine group.

An observational comparison was made between the efficacy observed in the subset aged >26 and ≤32 weeks at the time of the third dose and the efficacy estimated previously for the overall efficacy population.

For the healthcare resource utilisation (HCRU) analysis of data from study 006, estimates of the rate reduction for the incidence of hospitalisations and ER visits and the corresponding 95% confidence intervals were computed, based on the exact binomial method for ratios of Poisson counts.

Protocol violators excluded from the per-protocol population included (1) subjects who missed any of the 3 study vaccinations (2) subjects who did not have at least 28 days between study vaccinations (3) subjects who received a mixed regimen of study materials (4) subjects for whom the treatment arm was prematurely unblinded (5) subjects for whom there was a temperature excursion among administered vials/tubes of RotaTeq / placebo and (6) subjects who received more than 3 doses of the same vaccination material. In addition, subjects were classified as unevaluable for the analysis due to wild-type rotavirus prior to 14 days Post-dose 3, incomplete clinical and/or laboratory results or stool samples collected outside of the protocol-specified day range.

2.2.2. Results

Across studies 006 and 007 the numbers in the efficacy analyses who were aged > 26 and ≤ 32 weeks at the time of dose 3 are shown in the table. Recipients of RotaTeq and placebo were comparable with respect to gender, age at enrolment and race.

Table 1: Number of Subjects > 26 to ≤ 32 Weeks of Age at Dose 3 (006 and 007)

	RotaTeq	Placebo	Total
006 Efficacy Analysis	506	498	1,004
007 Efficacy Analysis	58	61	119
Total in Efficacy Analysis	**564**	**559**	**1,123**
006 with HCRU Outcome	**8,348**	**8,395**	**16,743**

In the combined primary per-protocol analysis of efficacy against any severity RVGE caused by G1, G2, G3 and G4 (see next table) the efficacy estimate was 61.5% (14.2%, 84.2%). However, the estimates varied from 56.8% in 006 to 79% in 007. It should be noted that the actual numbers of cases underlying these estimates was relatively small and the 95% CI are very wide.

The pooled study estimate (61.5%) was lower than the efficacy that was observed (and reported previously) in the overall population by study, being 74.0% (66.8%, 79.9%) in 006, 72.5% (50.6%, 85.6%) in 007 and 73.8% (67.2%, 79.3%) in the combined studies.

Table 2: Efficacy by study and combined for 006 and 007 in subjects aged > 26 to ≤ 32 weeks at Dose 3

	006[†]		007		Combined Protocols	
	RotaTeq™[‡]	Placebo	RotaTeq™[‡]	Placebo	RotaTeq™[‡]	Placebo
Subjects contributing to efficacy analysis	441	451	52	55	493	506
Days of efficacy follow-up	116949	119932	7770	8175	124719	128107
Subjects classified as rotavirus gastroenteritis cases	8	19	1	5	9	24
Efficacy estimate (%) and 95% confidence interval	56.8 (-3.3, 83.6)	---	79.0 (-88.0, 99.6)	---	61.5 (14.2, 84.2)	---

[†] In 006, cases occurring at least 14 days Post-dose 3 through the first rotavirus season that began at least 14 days post-vaccination are evaluated.
[‡] In 006, RotaTeq was administered at the range of release potencies (≈ 6.5×10^7 to 1.2×10^8 infectious units/dose); In 007, RotaTeq was administered at expiry potency (≈ 1.1×10^7 infectious units/dose).
NOTE: Rotavirus gastroenteritis cases consist of all subjects with one or more episodes classified as positive. Multiple positive episodes for one subject are counted as a single case, and the first positive episode is used as the date of the case.

The combined efficacy against severe RVGE caused by G1, G2, G3 and G4 was 100% (-150.9%, 100%). However, in this subset analysis there were only 3 cases of severe RVGE, all of which occurred in the placebo group. The corresponding analysis for severe RVGE due to any virus type gave the exact same numbers.

Table 3: Efficacy vs. G1, G2, G3 and G4 Severe RVGE (Severity Score >16) in the PP Population and using the PP Case Definition in subjects aged > 26 to ≤ 32 weeks at Dose 3

	006		007		Combined	
	RotaTeq	Placebo	RotaTeq™‡	Placebo	RotaTeq	Placebo
Subjects contributing to efficacy analysis	439	448	51	55	490	503
Days of efficacy follow-up	116995	120753	7695	8500	124690	129253
Subjects classified as rotavirus gastroenteritis cases	0	2	0	1	0	3
Efficacy estimate (%) and 95% confidence interval	100 (-449.6, 100)	---	100 (-4208.0, 100)	---	100 (-150.9, 100)	---

The combined efficacy against any severity RVGE and regardless of serotype was 58.2% (13.0%, 81.3%). Again, the estimate was much lower in 006 than in 007 and the total (pooled) number of cases was only 38 (11 RotaTeq and 27 placebo). This pooled estimate is lower than the efficacy observed in the overall population, being 71.8% (64.5%, 77.8%) in 006, 72.7% (51.9%, 85.4%) in 007 and 72.0% (65.3%, 77.5%) for combined data.

Table 4: Efficacy vs. all RVGE (PP Population and Case Definition) in those aged >26 to ≤32 weeks at Dose 3

	006		007		Combined Protocols	
	RotaTeq	Placebo	RotaTeq	Placebo	RotaTeq	Placebo
Subjects contributing to efficacy analysis	441	450	52	55	493	505
Days of efficacy follow-up	116443	119181	7770	8138	124213	127319
Subjects classified as cases	10	21	1	6	11	27
Efficacy estimate (%) and 95% confidence interval	51.3 (-8.1, 79.5)	---	82.5 (-43.9, 99.6)	---	58.2 (13.0, 81.3)	---

All subjects in 006 were followed for 2 years post-vaccination to capture hospitalisations and ER visits for RVGE. The HCRU analysis of G1, G2, G3 and G4 RVGE (see next table) gave a rate reduction estimate of 89.4% (56.8%, 98.8%) for hospital and ER visits. This result was comparable to those obtained in the overall population of this study (94.5% [91.2%, 96.6%]) for hospitalisation and ER visits, 95.8% ([90.5%, 98.2%]) for hospitalisations and 93.7% ([88.8%, 96.5%]) for ER visits.

The corresponding analysis based on RVGE of any virus type gave the exact same figures.

Table 5: Hospital Admissions and ER Visits for G1, G2, G3 and G4 RVGE (PP population and PP case definition) in subjects aged >26 to ≤ 32 weeks at dose 3 (study 006)

	RotaTeq	Placebo
Subjects contributing to analysis	6878	6941
Hospital admissions and Emergency department visits		
Number of events (rate of events)[†]	2 (0.5)	19 (4.9)
Rate reduction and 95% confidence interval	89.4% (56.8%, 98.8%)	---
Hospital admissions		
Number of events (rate of events)[†]	1 (0.3)	9 (2.3)
Rate reduction and 95% confidence interval	88.8% (20.6%, 99.8%)	---
Emergency department visits		
Number of events (rate of events)[†]	1 (0.3)	10 (2.6)
Rate reduction and 95% confidence interval	89.9% (30.4%, 99.8%)	---
[†] The rates of events represent the incidence density and are expressed as the annual number of events per 1000 person years.		

The MAH's conclusions from these analyses are as follows:

- RotaTeq showed efficacy against any severity RVGE in subjects aged >26 to ≤32 weeks at Dose 3.
- Based on limited data, the vaccine appeared to have positive efficacy against severe RVGE in subjects aged >26 to ≤32 weeks at Dose 3.
- RotaTeq reduced the rate of hospitalisations and ER visits for RVGE in subjects aged >26 to ≤32 weeks at Dose 3.
- The data support the use of the third dose of RotaTeq between 26 and 32 weeks of age.

Analyses for the subjects aged > 26 up to 32 weeks at the time of the third dose

The MAH was requested during the procedure to provide analyses for the subjects aged > 26 up to 32 weeks at the time of the third dose based on all cases of RVGE regardless of the PP case definition and also all cases of RVGE regardless of whether or not subjects met the PP population criteria. The MAH was also requested to show all cases of RVGE that occurred after the second dose was administered and from 14 days after the second dose.

The MAH stated that the PP approach evaluated efficacy starting from Dose 3 + 14 days and excluded subjects who were protocol violators. In the context of evaluating subjects who were >26 up to 32 weeks of age at Dose 3, the relevant starting point is Dose 3 and the relevant population is all subjects who were vaccinated with 3 doses (and were >26 up to 32 weeks of age at Dose 3).

Because the vast majority of protocol violations involved receipt of < 3 doses, the MAH clarified that "PP population" and the "relevant population regardless of PP criteria" is essentially the same. From

Dose 3 to before 14 days following Dose 3 there were no cases of RVGE in recipients of RotaTeq and only one case in the placebo group (Table 6). From Dose 2 to before Dose 3, there were 4 cases of RVGE in recipients of RotaTeq and 6 in the placebo group. From 14 days after Dose 2 to before Dose 3, there were 2 cases of RVGE in recipients of RotaTeq group and 2 cases in the placebo group.

Table 6: Distribution of G1, G2, G3, and G4 Serotype Rotavirus Gastroenteritis Cases of Any Severity for Specific Day Ranges Occurring Through the First Rotavirus Season Post-vaccination Among Subjects Vaccinated with at Least One Dose, Among Subjects Between Older than 26 to at Most 32 Weeks of Age at Dose 3

	Protocol 006		Protocol 007		Combined Protocols	
	RotaTeq™‡	Placebo	RotaTeq™‡	Placebo	RotaTeq™‡	Placebo
From Dose 3 to Before 14 Days Following Dose 3	0	0	0	1	0	1
From Dose 2 to Before Dose 3	4	6	0	0	4	6
From 14 Days After Dose 2 to Before Dose 3	2	2	0	0	2	2

‡ In Protocol 006, RotaTeq™ was administered at the range of release potencies (≈ 6.5×10^7 to 1.2×10^8 infectious units/dose); In Protocol 007, RotaTeq™ was administered at expiry potency(≈ 1.1×10^7 infectious units/dose).
NOTE: Rotavirus gastroenteritis cases consist of all subjects with one or more episodes classified as positive. Multiple positive episodes for one subject are counted as a single case, and the first positive episode is used as the date of the case.

An analysis regardless of the PP case definition and PP population criteria but using the general criteria for evaluating efficacy starting from Dose 1 is also provided (Table 7). Note that the distribution of cases in Table 6 is derived from the analysis displayed in Table 7.

Table 7: Efficacy Analysis of G1, G2, G3, and G4 Serotype Rotavirus Gastroenteritis Cases of Any Severity Occurring Through the First Rotavirus Season Post-vaccination Among all Subjects Vaccinated with at Least One Dose, Among Subjects Between Older than 26 to at Most 32 Weeks of Age at Dose 3

	Protocol 006		Protocol 007		Combined Protocols	
	RotaTeq™‡	Placebo	RotaTeq™‡	Placebo	RotaTeq™‡	Placebo
Subjects contributing to efficacy analysis	415	424	55	57	470	481
Days of efficacy follow-up	164965	167947	15462	16053	180427	184000
Subjects classified as cases	18	29	2	6	20	35
Efficacy estimate (%) and 95% confidence interval	36.8 (-17.7, 67.0)	---	65.4 (-93.5, 96.6)	---	41.7 (-3.8, 68.1)	---

‡ In Protocol 006, RotaTeq™ was administered at the range of release potencies (≈ 6.5×10^7 to 1.2×10^8 infectious units/dose); In Protocol 007, RotaTeq™ was administered at expiry potency(≈ 1.1×10^7 infectious units/dose).
NOTE: Rotavirus gastroenteritis cases consist of all subjects with one or more episodes classified as positive. Multiple positive episodes for one subject are counted as a single case, and the first positive episode is used as the date of the case.

Tables 8 and 9 are similar to Tables 6 and 7, respectively, but include all serotypes.

Table 8 Distribution of Rotavirus Gastroenteritis Cases of Any Serotype, Any Severity for Specific Day Ranges Occurring Through the First Rotavirus Season Post-vaccination Among all Subjects Vaccinated with at Least One Dose, Among Subjects Between Older than 26 to at Most 32 Weeks of Age at Dose 3

	Protocol 006		Protocol 007		Combined Protocols	
	RotaTeq™‡	Placebo	RotaTeq™‡	Placebo	RotaTeq™‡	Placebo
From Dose 3 to Before 14 Days Following Dose 3	0	1	0	1	0	2

From Dose 2 to Before Dose 3	5	6	0	0	5	6
From 14 Days After Dose 2 to Before Dose 3	3	2	0	0	3	2

‡ In Protocol 006, RotaTeq™ was administered at the range of release potencies (≈ 6.5×10^7 to 1.2×10^8 infectious units/dose); In Protocol 007, RotaTeq™ was administered at expiry potency(≈ 1.1×10^7 infectious units/dose).
NOTE: Rotavirus gastroenteritis cases consist of all subjects with one or more episodes classified as positive. Multiple positive episodes for one subject are counted as a single case, and the first positive episode is used as the date of the case.

Table 9 Efficacy Analysis of Rotavirus Gastroenteritis Cases of Any Serotype, Any Severity Occurring Through the First Rotavirus Season Post-vaccination Among all Subjects Vaccinated with at Least One Dose, by Protocol and Across Protocols Among Subjects Between Older than 26 to at Most 32 Weeks of Age at Dose 3

	Protocol 006		Protocol 007		Combined Protocols	
	RotaTeq™‡	Placebo	RotaTeq™‡	Placebo	RotaTeq™‡	Placebo
Subjects contributing to efficacy analysis	417	425	55	57	472	482
Days of efficacy follow-up	164667	167175	15129	16016	179796	183191
Subjects classified as cases	22	33	3	7	25	40
Efficacy estimate (%) and 95% confidence interval	32.3 (-19.6, 62.4)	---	54.6 (-98.7, 92.4)	---	36.3 (-7.6, 63.0)	---

‡ In Protocol 006, RotaTeq™ was administered at the range of release potencies (≈ 6.5×10^7 to 1.2×10^8 infectious units/dose); In Protocol 007, RotaTeq™ was administered at expiry potency(≈ 1.1×10^7 infectious units/dose).
NOTE: Rotavirus gastroenteritis cases consist of all subjects with one or more episodes classified as positive. Multiple positive episodes for one subject are counted as a single case, and the first positive episode is used as the date of the case.

2.2.3. Discussion on efficacy

Across studies 006 and 007 the numbers in the efficacy analyses who were aged >26 and ≤32 weeks at the time of dose 3 exceeded 500 per treatment group but there were only ~60 per group in study 007. The analyses presented focus on RVGE that occurred at least 14 days after the last dose in the PP population and using the PP case definition. The estimates of efficacy against RVGE due to vaccine types and any rotavirus types both showed a difference between the two studies such that efficacy was higher in 007 but this was based on a very few cases and is considered to be unreliable. In 006, where the estimates of efficacy were based on larger numbers of cases, the point values were lower than reported previously for the overall population while the 95% CI were very wide and spanned zero. There were too few severe cases to make any comment.

It is only the study 006 HCRU analysis that suggested that the effect of vaccination was comparable between the total study population and the subset of subjects who were at the upper end of the age range when the last dose was administered. This analysis is based on only 21 events but the 95% CI do support a benefit for RotaTeq use under these circumstances.

The analyses are all based on the PP population and PP case definition.

The results presented initially in this application were based on the subset that received the third dose between weeks 26 and 32, counting cases that met the PP case definition that occurred from 14 days after the third dose. These results showed some disadvantage for delaying the third dose as follows:

- Efficacy against any severity RVGE caused by G1, G2, G3 and G4 was estimated at 61.5% (14.2%, 84.2%). However, the estimates varied from 56.8% in 006 to 79% in 007 (with very wide 95% CI). This pooled study estimate (61.5%) was lower than those for the overall population (74.0% in 006, 72.5% in 007 and 73.8% in the combined studies).
- Efficacy against any severity RVGE and regardless of serotype was 58.2%, which was much lower than the efficacy observed in the overall population (71.8% in 006, 72.7% in 007 and 72.0% for combined data).
- The HCRU analysis of G1, G2, G3 and G4 RVGE gave a rate reduction estimate of 89.4% (56.8%, 98.8%) for hospital and ER visits, which was near to the estimates obtained in the overall population (95.8% for hospitalisations and 93.7% for ER visits). The corresponding analysis based on RVGE of any virus type gave the exact same figures.

On the basis of these initial analyses it seemed that efficacy was lower when the third dose was delayed.

The additional analyses that also show the numbers of cases that occurred between doses 2 and 3 underline this concern. Overall, delaying the third dose beyond week 26 should be conveyed as the exception and not a routinely acceptable regimen.

2.3. Clinical Safety aspects

2.3.1. Methods – analysis of data submitted

Statistical Analysis Plan - combined safety analysis of data from studies 006, 007 and 009

The objective was to evaluate the risk of IS among recipients of RotaTeq relative to placebo within 42 days following the third dose when this last dose was administered between 26 and 32 weeks of age.

The primary safety endpoint was confirmed IS within 42 days following the third dose of RotaTeq or placebo in the subset of subjects aged > 26 to ≤ 32 weeks at the time of the last vaccination. The following endpoints were also summarised:

- Confirmed IS that occurred within 7, 14 and 60 days Post-dose 3
- Adverse experiences of special clinical interest: diarrhoea, elevated temperatures, irritability and vomiting that occurred within 7 days Post-dose 3
- Adverse experience of haematochezia that occurred within 42 days Post-dose 3

The safety data across studies 006, 007 and 009 were combined. The relative risk of IS was the incidence in the vaccine group divided by the incidence in the placebo group. An estimate of relative risk and associated 95% confidence interval was calculated. The confidence interval was based on a binomial distribution for the number of subjects with IS in the vaccine group relative to the total number of subjects with intussusception, formed by conditioning on the total number of subjects with intussusception. The confidence limits for relative risk were then computed based on the relationship relative risk = p/(1-p), where p was the corresponding parameter of interest from the binomial distribution.

For the analysis of the other AEs, risk differences (RotaTeq minus placebo) were calculated for the proportions of subjects with the AEs, along with associated 95% confidence intervals around the differences and p-values. The confidence intervals and p-values for the differences were based on an

exact binomial approach. An observational comparison of the result of >26 and ≤32 weeks of age at Dose 3 analysis with the result of the overall group analysis was also performed.

All subjects (Safety Cohort) were evaluated for potential cases of IS and SAEs. Subjects in the Detailed Safety Cohort of study 006 and all subjects in 007 and 009 were evaluated with respect to all clinical AEs that occurred within 42 days following any vaccination.

Statistical Analysis Plan – study 019

The primary objective of 019 was to compare the observed incidence of IS within 30 days after infants received one or more doses of RotaTeq to the expected incidence of IS derived from the historical data using a statistical monitoring boundary. A secondary objective was to compare the incidence of IS in children who received RotaTeq to that in the concurrent control cohort composed of children not vaccinated with RotaTeq, matched by date of birth. The analysis was based on the concurrent control cohort.

Available person-time was determined within the 0 to 30 day window following each dose. Person-time of follow-up was censored within the follow-up window upon the occurrence of a subsequent dose of a relevant vaccination, occurrence of a study outcome, study withdrawal or the infant reaching one year of age. The initial claims-based event date was replaced by the actual event date for chart-confirmed cases of IS if they were different. Potential cases IS were confirmed through searching cohort insurance claims for qualifying diagnosis or procedure codes from hospitals or ERs. Medical records were sought and there was adjudication of the diagnosis by an independent Adjudication Committee (AC) composed of three clinicians.

Calculations were conducted for incidence rates of chart-confirmed events (events divided by person-time), exact 95% confidence intervals (CI) and associated relative risks (RR), along with one-sided non-mid-p exact probabilities.

Relative risks associated with RotaTeq were estimated by comparing the incidence of outcomes in the 30 days following administration of any dose to the incidence derived from the 30 days subsequent to DTaP in the concurrent cohort of infants not vaccinated with RotaTeq. The RR was calculated by stratifying IS by the age of receipt of the third doses at <= 32 week and > 32 weeks of age and also at <= 26 weeks or > 26 weeks of age. For this analysis by age, the cohort of children receiving the third dose of RotaTeq was compared to concurrent DTaP controls that received DTaP in the same age category.

Vaccinated Cohorts were:

1. *Prospective RotaTeq cohort*: On a quarterly basis, all infants vaccinated with RotaTeq were identified in the claims database from the 1Q2006 through end 4Q2007 using the Current Procedural Terminology (CPT) code for oral rotavirus vaccine (90680 Rotavirus vaccine, pentavalent, 3 dose schedule, live, for oral use).
2. *Concurrent DTaP control cohort*: Applying the same eligibility criteria the concurrent DTaP infants were identified on a quarterly basis using CPT codes for DTaP vaccination. If a concurrent DTaP infant had a subsequent claim for RotaTeq then follow-up time of the infant was censored as of the date of vaccination and the infant entered into the RotaTeq cohort. A replacement concurrent DTaP infant was then selected from the pool of eligible comparators. The cohort included all infants first vaccinated with RotaTeq and DTaP in 2007.

2.3.2. Results

Combined safety analysis

A summary of the number of subjects who received the third dose of RotaTeq or placebo at >26 to ≤32 weeks of age is provided in the next table. Numbers are based on the group to which the subject was randomised. Recipients of RotaTeq and placebo were comparable with respect to gender, age at enrolment and race.

Table 10: Number for Combined Safety Analysis aged >26 to ≤32 Weeks at Dose 3 (006, 007 and 009)

	RotaTeq™	Placebo
Protocol V260-006	8,348	8,395
Protocol V260-007	58	61
Protocol V260-009	474	82
Total:	**8,880**	**8,538**

There were no positively-adjudicated (confirmed) cases of intussusception in 007 or 009.

In 006 one case of confirmed IS occurred within 42 days of dose 3 among subjects aged >26 to ≤32 weeks of age at Dose 3. This subject had confirmed IS on Day 40 Post-dose 3 of RotaTeq. The subject was a Hispanic-American female aged 2 months when enrolled. On Day 22 Post-dose 3, the subject was taken to the ER and admitted to the hospital with blood and mucous in her stool. A stool specimen was negative for rotavirus and a stool culture was negative. A metabolic panel was within normal limits. On Day 23 Post-dose 3 she was discharged from the hospital with a diagnosis of gastroenteritis.

Subsequently, on Day 40 Post-dose 3, the subject was brought back to the ER and was admitted to the hospital due to reports of bright red blood and an increase in the amount of mucous in her stools, constipation, abdominal pain and intermittent pyrexias. The signs and symptoms were consistent with total colon IS as suspected clinically from a protruding rectal mass. A barium enema confirmed IS and reduction was attempted using a barium enema. The mass was successfully reduced from the rectal region into the caecum but complete reduction was not possible. Exploratory laparotomy confirmed IS within the caecum and partial reduction was accomplished but perforation of the terminal ileum occurred so that a segmental resection of the terminal ileum and caecum was performed with ileal colostomy and appendectomy.

On Day 45 Post-dose 3, the subject was discharged from the hospital and was considered to be recovered. The blinded investigator determined that the serious adverse experiences of gastroenteritis and intussusception were possibly related to RotaTeq.

There were 5 confirmed cases of IS that occurred at any time Post-dose 3 in subjects aged > 26 to ≤ 32 weeks at Dose 3, of which 2 received RotaTeq (see next table). In addition to the subject described above, the other case in the RotaTeq group concerned a subject who died due to confirmed IS on Day 96 Post-dose 3 and sepsis on Day 99 Post-dose 3. The investigator determined that the intussusception and sepsis were probably not related to study vaccine.

Table 11: Confirmed IS following dose 3 in subjects aged >26 to ≤32 weeks at Dose 3 (Safety Cohort - 006)

Vaccine	M/F	Race	Age at First Vaccination	Relative Day from Start of Trial	Relative Day of Onset Postdose	Adverse Experience	Duration of Adverse Experience	Intensity /Size †	Vaccine Relation-ship	Action Taken	Outcome
RotaTeq	M	white	9 wk	218	96	**Intussusception**	4 day	severe	prob not	none	fatal
				221	99	Sepsis	8.5 hr	severe	prob not	none	fatal
	F	Hispa	10 wk	146	22	Gastroenteritis	2 day	mod	poss	none	recovered
				164	40	**Intussusception**	6 day	severe	poss	none	recovered
Placebo	M	black	9 wk	225	97	**Intussusception**	3 day	severe	def not	none	recovered
	M	white	9 wk	604	456	**Intussusception**	6 day	severe	def not	none	recovered
	M	multi	9 wk	292	165	**Intussusception**	5 day	mod	prob not	none	recovered

There were also 9 non-confirmed cases of IS that occurred at any time Post-dose 3 in study 006 among subjects aged >26 to ≤32 weeks at Dose 3. Three of the 9 cases had received RotaTeq and had non-confirmed IS within 42 days Post-dose 3. There were also 5 subjects in 007 and 2 in 009 who were medically evaluated for possible IS and one who received RotaTeq was aged >26 to ≤32 weeks at Dose 3.

In the three studies and total study populations there were 17 subjects (7 RotaTeq) who experienced an AE resulting in death following Dose 3. This number included 5 subjects (2 RotaTeq) aged >26 weeks to ≤32 weeks at Dose 3 and one of the two in the RotaTeq group was the subject mentioned above with IS and sepsis. The other RotaTeq recipient died on Day 16 Post-dose 3 with a cause of death initially reported as neonatal ("positional") asphyxia (similar to SIDS) probably not related to study vaccine. The AE was later changed to death of unknown cause as the coroner found some evidence of pneumonia and could not define the cause of death as SIDS. Since the coroner was unable to exclude an association with the study vaccine the assessment of causality was changed to possibly vaccine related.

No subjects discontinued due to a clinical AE from Day 1 to Day 42 following Dose 3.

AEs of special interest were to be recorded on the vaccination report card (VRC) for the first 7 days following any dose for subjects in the Detailed Safety Cohort of study 006 and subjects in 007 and 009. Among all these subjects there was no evidence of a difference between RotaTeq and placebo for rates of AEs of special clinical interest following Dose 3.

In the subset aged >26 to ≤32 weeks at Dose 3 who reported AEs of special clinical interest within 7 days Post-dose 3 the next table shows rates that were comparable between the RotaTeq and placebo groups or (for diarrhoea) were slightly numerically higher as was observed in the entire Detailed Safety Cohort in study 006. Number (%) aged >26 to ≤32 weeks at Dose 3 with AEs of special interest within 7 Days Post-dose 3 in 006 [Detailed Safety Cohort], 007 and 009

Table 12:

	RotaTeq			Placebo		
	n	m	%	n	m	%
Diarrhoea						
Postdose 3	164	1986	8.3	103	1580	6.5
Elevated Temperature						
Postdose 3	432	1621	26.7	330	1244	26.5
Irritability						
Postdose 3	78	1986	3.9	62	1580	3.9
Vomiting						
Postdose 3	97	1986	4.9	62	1580	3.9
m = Number of subjects with follow-up. n = Number of subjects with adverse experience.						

In 007 and 009 haematochezia was summarised in the CSR if reported within 42 days after a dose or as a SAE. In study 1.2% RotaTeq and 0.9% placebo group subjects reported haematochezia as a non-serious AE and one in the placebo group reported haematochezia as a SAE 38 days Post-dose 3. In 009, 0.4% RotaTeq and no placebo group subjects reported haematochezia.

In the Detailed Safety Cohort of study 006 haematochezia was evaluated as an AE of special clinical interest within 42 days following each dose. Four of the 9 subjects who reported haematochezia as an AE within 42 days post-dose 3 had received RotaTeq. However, only two aged > 26 to ≤ 32 weeks at Dose 3 reported haematochezia as an AE within 42 days post-dose 3 and only one of these received RotaTeq

The MAH's conclusions from the combined safety analysis are as follows:

1. Among subjects who were > 26 to ≤ 32 weeks of age at Dose 3, the results suggest that there is no evidence of excess risk of intussusception associated with RotaTeq following Dose 3 when Dose 3 is administered between 26 to 32 weeks of age.
2. There is no evidence of a difference between RotaTeq and placebo with respect to the incidences of adverse experiences of special clinical interest (diarrhoea, elevated temperature, irritability and vomiting) within 7 days following Dose 3 in subjects who were > 26 to ≤ 32 weeks of age at Dose 3.
3. There is no evidence of a difference between the group that received RotaTeq and the group that received placebo with respect to the incidence of haematochezia within 42 days following Dose 3 in subjects who were > 26 to ≤ 32 weeks of age at Dose 3.

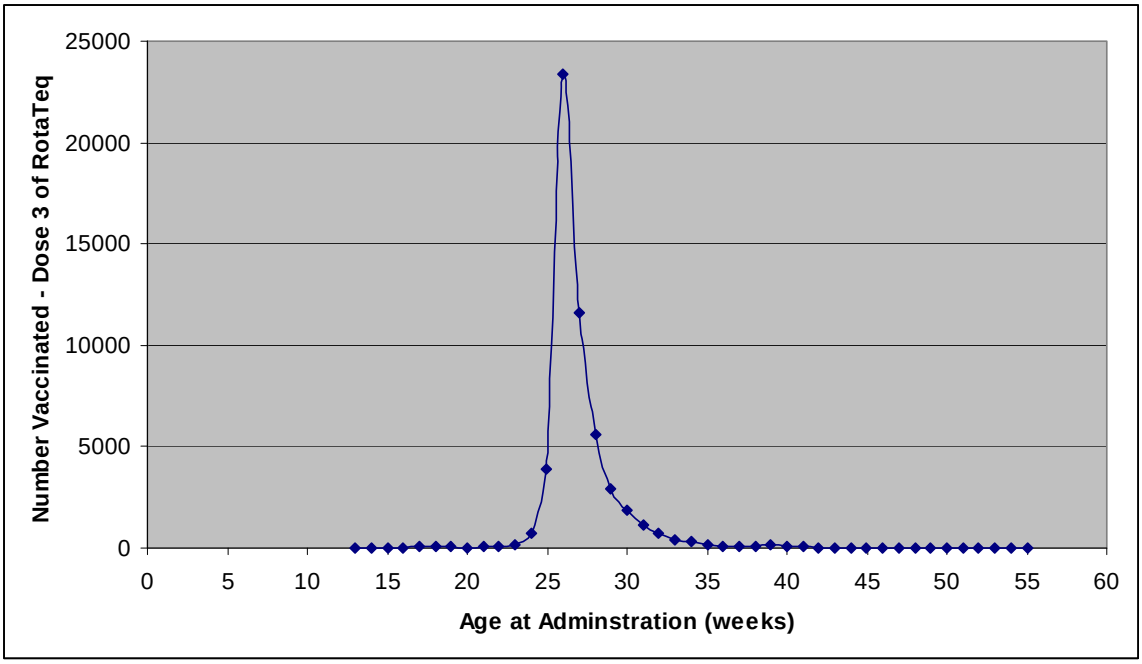
Results – study 019

The study identified 85,150 infants vaccinated with RotaTeq (over 210,000 doses) in the 2-year accrual period, contributing 17,433 person-years of follow-up within 30 days. The 62,617 concurrent DTaP controls contributed 12,339 person-years of follow-up within 30 days. The infants in the two cohorts were comparable with respect to age at first dose and proportion receiving subsequent doses. Among the infants that received at least one dose of RotaTeq there were 70,998 who received a second dose and 53,923 had received a third dose by the end of follow-up in March 2009.

For the 0 to 30 day follow-up window following any dose, there were 6 confirmed cases of IS among infants vaccinated with RotaTeq, which gives an incidence rate of 0.3 per 1000 person-years (95% CI: 0.13, 0.75) compared with 5 cases among the concurrent controls vaccinated with DTaP for an incidence rate of 0.4 per 1000 person-years (95% CI: 0.13, 0.95) (RR of intussusception = 0.8, 95% CI: 0.22, 3.52).

The figure below shows the distribution by week of age of vaccinated infants who received the third dose of RotaTeq. By the end of the study follow-up in period, 53,923 infants had received a third dose. Of these, 28,549 (52.9%) infants received the third dose at ≤ 26 weeks of age and 25,374 (47.1%) infants received the third dose at ages greater than 26 weeks.

Figure 1: Distribution of infants who received the 3rd dose of RotaTeq by age (weeks) - Claims-Based Data



The table below shows that when Dose 3 was administered at ≤ 26 weeks of age there were no confirmed cases of IS in the 30-day follow-up period in the RotaTeq or control groups. When Dose 3 was administered at > 26 weeks of age there was one case only and this occurred in the control group.

The corresponding analysis based on Dose 3 administration at ≤ 32 or > 32 weeks of age showed no cases when the dose was given after week 32 and the single case in the control group when it was given before 32 weeks of age.

Table 13: Rate of Chart-Confirmed IS (per 1000 Person-Years) in the 0-30 Day Follow-up Window, Administration of Doses 1 and 3 by Age[1]

Follow-Up Window (days)	Vaccine Dose	RotaTeq Infants (n=85,150) N Chart Cases	Person-years	Rate	95% Confidence Interval	Concurrent DTaP Controls[2] (n=62,617) N Chart Cases	Person-years	Rate	95% Confidence Interval	Relative Risk[3]	95% Confidence Interval	One-Sided P Value[4]
Dose One ≤ 12 Weeks												
0 - 30	Any	4	16,198	0.2	0.07 - 0.63	4	10,797	0.4	0.10 - 0.95	0.7	0.12 - 3.58	0.406
Dose One > 12 Weeks												
0 - 30	Any	2	1,235	1.6	0.20 - 5.85	1	1,541	0.6	0.02 - 3.61	2.5	0.13 - 147.31	0.417
Dose One ≤ 12 Weeks												
0 - 30	One	2	6,358	0.3	0.04 - 1.14	2	4,312	0.5	0.06 - 1.68	0.7	0.05 - 9.36	0.532
Dose One > 12 Weeks[5]												
0 - 30	One	2	691	2.9	0.35 - 10.46	1	873	1.1	0.03 - 6.38	2.5	0.13 - 149.16	0.413
Dose Three ≤ 26 Weeks												
0 - 30	Three	0	2,374	0.0	0.00 - 1.26	0	1,414	0.0	0.00 - 2.12			.
Dose Three > 26 Weeks												
0 - 30	Three	0	2,117	0.0	0.00 - 1.42	1	1,605	0.6	0.02 - 3.47	0.0	0.00 - 29.57	0.431
Dose Three ≤ 32 Weeks												
0 - 30	Three	0	4,361	0.0	0.00 - 0.69	1	2,751	0.4	0.01 - 2.03	0.0	0.00 - 24.60	0.387
Dose Three > 32 Weeks												
0 - 30	Three	0	130	0.0	0.00 - 23.04	0	269	0.0	0.00 - 11.15			

[1] Label-recommended dosing schedule for RotaTeq (US): administration of Dose 1 at age 6-12 weeks, Doses 2 and 3 at 4- to 10-week intervals, Dose 3 by 32 weeks. Label-recommended dosing schedule for DTaP (US): administration of Dose 1 at 2 months of age, Doses 2 and 3 at 4 and 6 months.
[2] Infants with DTaP vaccination in 2006 were matched to RotaTeq infants on date of birth and dose.
[3] When both incidence rates = 0, relative risk, confidence interval, and p-value not calculated.
[4] One-sided non-midp exact probability, significant at p<0.025.
[5] Claims Dose 1 was validation Dose 2 for 2 RotaTeq infants, and claims Dose 1 was validation Dose 3 for 1 DTaP infant.

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Post-Marketing Safety Summary

The MAH's NWAES database was queried on May 12 2011 for spontaneous post-marketing reports received from Health Care Providers for the cumulative time period from market introduction (November 2005) up to March 31 2011. Additional criteria were added to narrow the search to identify patients with a vaccination at an age between 26 and 32 weeks. The criteria included all cases with the patient's birth date and vaccination date so that age at the time of vaccination could be calculated. Reports that had an estimated date of birth or vaccination were included.

There were 330 reports that involved a patient with an age between 26 to 32 weeks at the time of vaccination of which 154 (47%) were serious (including all reports of haematochezia). The reports originated from the United States (n=283), Australia (n=37), Germany (n=4) and Spain (n=3) with single reports from each from Greece, Nicaragua and Slovenia.

The most frequently reported serious adverse events were *Intussusception†* (86), Gastroenteritis rotavirus (20), *vomiting†* (20), dehydration (18), *diarrhoea†* (15), *haematochezia† (*14- from the time from market introduction through 01 March 2011, all reports of haematochezia were automatically upgraded to "serious" to ensure prompt regulatory reporting as part of a regulatory commitment), *pyrexia†* (13), gastroenteritis (6), irritability (5) and rotavirus infection (5). Five (denoted *†)*of these 10 events are listed in the CCDS.

The MAH states that the conclusions that can be drawn are subject to the limitations of post-marketing data. The number of reports in which the age of the patient at the time of vaccination could be determined was relatively small (1853) compared to the total number of reports in the database (5272). The denominator (number of doses administered to infants between the ages of 26-32 weeks)

is unknown. However, in over five years of post-marketing experience, no new safety concerns have been identified in this patient population.

2.3.3. Discussion on clinical safety

The CHMP considered that the clinical safety data from the studies discussed did not raise any specific concerns in view of IS or overall safety when the 3rd dose of Rotateq is given 26-32 weeks of age. Concerning the available post marketing data, also no specific safety signal could be detected up to 32 weeks of age, however the CHMP noted that the number of reports in which the age of the patient at the time of vaccination could be determined was relatively small. Although the size of the safety database is limited for this population, the CHMP acknowledged that in over five years of post-marketing experience no new safety concern has arisen in infants that received the 3rd dose of the vaccine at 26-32 weeks of age.

2.4. Risk management plan

The CHMP, having considered the data submitted, was of the opinion that no new pharmacovigilance activities in addition to those already being performed were needed to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

2.5. Changes to the Product Information

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed:

SmPC

Section 4.2: Posology and method of administration

Posology
(...)

From 6 weeks to ~~26~~ 32 weeks

The vaccination course consists of three doses.

The first dose may be administered from the age of 6 weeks and no later than the age of 12 weeks.

RotaTeq may be given to infants who were born prematurely provided that the period of gestation was at least 25 weeks. These infants should receive the first dose of RotaTeq at least six weeks after birth (see sections 4.4 and 5.1).

There should be intervals of at least 4 weeks between doses.

It is preferable that t~~T~~he vaccination course of three doses should ~~preferably~~ be ~~given~~ completed by the age of 20-22 weeks. If necessary, the third (last) dose may be given up to the age of 32 weeks (see section 5.1). ~~before the age of 20-22 weeks, and should be completed by the age of 26-32 weeks.~~

(…)

From ~~26~~ 33 weeks to 18 years

RotaTeq is not indicated in this subset of paediatric population.

(…)

Section 5.1 Pharmacodynamic properties

(…)

In a combined post-hoc analysis of REST and another phase III study, the vaccine efficacy against G1-, G2-, G3- and G4-serotype RVG cases (any severity) was 61.5 % [95 % CI: 14.2; 84.2] among infants who were >26 to ≤32 weeks of age at dose 3.

During the procedure, the CHMP requested the following additional amendments to the Product Information:

Section 4.2:

The initial wording proposed by the MAH, which deleted the preference for the 3rd dose up to week 20-22, was revised to reflect that the vaccination course of three doses should be completed by the age of 20-22 weeks. If necessary, the third (last) dose may be given up to the age of 32 weeks.

Section 4.8

Wording initially proposed by the MAH on analyses up to 32 weeks of age were considered not relevant or supported by data and therefore deleted.

Section 5.1:

Wording proposed by the MAH on the administration of third dose of vaccine or placebo in the study was deleted as the efficacy data in those who received the last dose after age 26 weeks suggest a lower estimate of efficacy and since the age-specific efficacy is not shown.

Furthermore, the wording on the study results was revised as it was not acceptable to pool the data and efficacy was not wholly consistent with that for the entire study populations. Also, a statement regarding severe RVGE was removed since no conclusions could be drawn from the cases

Changes were also made to the Labelling to bring it in line with the current guidance on Braille which were reviewed and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of Czech Republic, Estonia, Hungary and Slovakia.

3. Overall conclusion and impact on the benefit/risk balance

The CHMP considers that the efficacy data suggest that it is not ideal to delay administration of the third dose, however that it was useful to revisit the rationale for the initial (and current) recommendation in the SmPC that the 3-dose schedule should be completed preferably by week 22 and no later than week 26.

This procedure was predominantly driven by the actual mean age at the time of the last dose in the Phase III pre-licensure studies. It was secondarily influenced by an attempt to complete all doses

before the peak age of naturally occurring intussusception in the EU in order to minimise the risk that naturally occurring IS could be wrongly attributed to the vaccine. In this regard the MAH has attempted to point out that the IS peak may occur even before week 26 but, in fact, the graphs show that completing all doses by week 22, as recommended to be preferable in the current SmPC, would still avoid dosing at the time of onset of peak incidence.

Most EU countries employ a 3-dose primary infant immunisation series for all routine antigens and, if used, the third dose of RotaTeq is likely to be administered at the same visit as the last of these doses i.e. at around 6 months or 24 weeks of age. This last visit may be delayed for more than 2 weeks for many possible reasons.

Therefore, and primarily for reasons of achieving a practical compromise, the CHMP agreed on a modified wording, which provides some additional latitude to the current dose recommendations. However at the same time, the new wording stresses the preference for adherence to the recommendations for completing dosing that were made at the time of initial approval. While delaying the last dose is not optimal, omitting the third dose simply because the child presents late is also not ideal. Since there is no clear evidence of a safety concern associated with a third dose at week 32 the compromise that has been agreed with respect to the SmPC is considered acceptable.

Overall, taking together the available efficacy and safety data, the CHMP considered that the benefit-risk remains positive when a 3rd dose is administered up to 32 weeks of age.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

To extend the upper limit of the administration of the third dose of vaccine from up to 26 weeks to up to 32 weeks of age.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to amend the section on Braille in the Labelling in line with current guidance.

The variation proposed amendments to the SmPC, Labelling and Package Leaflet.

Conditions and requirements of the marketing authorisation

Risk management system and PSUR cycle

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 5.0 of the Risk Management Plan (RMP) presented in Module 1.8.2.of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

Periodic Safety Reports (PSURS)

The MAH will continue to submit yearly PSURs, unless otherwise specified by the CHMP.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan (P/149/2011) and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.