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Procedure Management and Committees Support Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Synflorix

pneumococcal polysaccharide conjugate vaccine (adsorbed)

Procedure no: EMEA/H/C/000973/P46/058

Note

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

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1. Introduction

In October 2015, the MAH submitted a completed paediatric study for *Synflorix*, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The MAH stated that the data submitted do not influence the benefit-risk balance for *Synflorix*.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The applicant states that the study 'A phase III, open, controlled study to evaluate the immunogenicity, safety and reactogenicity of GSK Biologicals´10-valent pneumococcal conjugate vaccine administered to children with sickle-cell disease between 8 weeks and 2 years of age, as compared to healthy children' is a part of a clinical development program. A variation application consisting of the full relevant package (i.e. containing several studies to update the *Synflorix* product information with immunogenicity and safety data following administration of *Synflorix* in children with increased risk for pneumococcal infections) is expected to be submitted.

A line listing of all the concerned studies is annexed.

2.2. Clinical aspects

2.2.1. Introduction

The MAH has initiated a study to look at the active immunisation of infants and children from 6 weeks up to 5 years of age against disease caused by *Streptococcus pneumoniae* vaccine serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F and vaccine-related serotype 19A (including sepsis, meningitis, pneumonia, bacteraemia and acute otitis media) and against acute otitis media caused by non-typeable *Haemophilus influenzae*.

The MAH has submitted the final report for:

- study 10PN-PD-DIT-064 (*A phase III, open, controlled study to evaluate the immunogenicity, safety and reactogenicity of GSK Biologicals´10-valent pneumococcal conjugate vaccine administered to children with sickle-cell disease between 8 weeks and 2 years of age, as compared to healthy children*).

This study is part of the pediatric investigation plan (PIP) of Synflorix.

2.2.2. Clinical study

Study 10PN-PD-DIT-064

'A phase III, open, controlled study to evaluate the immunogenicity, safety and reactogenicity of GSK Biologicals´10-valent pneumococcal conjugate vaccine administered to children with sickle-cell disease between 8 weeks and 2 years of age, as compared to healthy children'.

Description

Methods

Objectives

Primary:

- To assess the immunogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine when co-administered with DTPw-HBV/Hib and OPV vaccines in children with SCD, one month after completion of the 3-dose primary vaccination course before 6 months of age.

Secondary:

- To assess the immunogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine when given as a 3-dose or 2-dose catch-up vaccination in children who were between 7 and 11 or between 12 and 23 months of age, respectively, at the time of first vaccination.
- To assess 5 to 6 months after the completion of the 3-dose primary vaccination course the persistence of antibodies induced by GSK Biologicals' 10-valent pneumococcal conjugate vaccine when co-administered with DTPw-HBV/Hib and OPV vaccines in children who received the primary vaccination course before 6 months of age.
- To assess one month post-booster vaccination, the immunogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine when co-administered with DTPw-HBV/Hib and OPV vaccines, in children who received the primary vaccination course before 6 months of age.
- To assess one month and 5 to 6 months after the completion of the primary vaccination course and one month post-booster, the immunogenicity of GSK Biologicals' DTPw-HBV/Hib vaccine when co-administered with the 10-valent pneumococcal conjugate vaccine and OPV in children who received the primary vaccination course before 6 months of age.
- To assess the safety and reactogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine when co-administered with DTPw-HBV/Hib and OPV vaccines as 3-dose primary vaccination before 6 months of age and as booster dose at 9-10 months of age.
- To assess 2 to 4 months after the completion of the 2-dose primary vaccination course, the persistence of antibodies induced by GSK Biologicals' 10-valent pneumococcal conjugate vaccine vaccines in children who were between 7 and 11 months of age at the time of first vaccination.
- To assess 2 to 4 months after the first dose, the persistence of antibodies induced by GSK Biologicals' 10-valent pneumococcal conjugate vaccine vaccines in children who were between 12 and 23 months of age at the time of first vaccination.
- To assess the safety and reactogenicity of GSK Biologicals' 10-valent pneumococcal conjugate vaccine when administered as a 3-dose or 2-dose catch-up vaccination in children who were between 7 and 11 or between 12 and 23 months of age, respectively, at the time of first vaccination.

Study design

This was a Phase III, open, single centre study with 6 parallel groups stratified according to age and sickle cell disease (SCD) status:

- **<6S group:** 8-11 week-old subjects with SCD receiving a 3-dose primary vaccination with 10Pn-PD-DiT vaccine at 8, 12 and 16 weeks of age and booster vaccination at 9-10 months of age*.
- **7-11S group:** 7-11 month-old subjects with SCD receiving a 2-dose primary vaccination with 10Pn- PD-DiT vaccine starting at 7-11 months of age and booster vaccination with an interval of 2 to 4 months since the previous dose.
- **12-23S group:** 12-23 month-old subjects with SCD receiving a 2-dose vaccination with 10Pn-PD-DiT vaccine with an interval of 2 to 4 months between doses.
- **<6NS group:** 8-11 week-old healthy subjects receiving a 3-dose primary vaccination with 10Pn-PD-DiT vaccine at 8, 12 and 16 weeks of age and booster vaccination at 9-10 months of age*.
- **7-11NS group:** 7-11 month-old healthy subjects receiving a 2-dose primary vaccination with 10Pn-PD-DiT vaccine starting at 7-11 months of age and booster vaccination with an interval of 2 to 4 months since the previous dose.
- **12-23NS group:** 12-23 month-old healthy subjects receiving a 2-dose vaccination with 10Pn-PD-DiT vaccine with an interval of 2 to 4 months between doses.

* Subjects in the <6S and <6NS groups received DTPw-HBV/Hib and oral poliovirus vaccine (OPV) as co-administered vaccines.

Notes:

- All subjects were allowed to receive through the local Expanded Program on Immunisation (EPI) Bacille-Calmette-Guérin (BCG) and OPV at birth, measles and yellow fever vaccines. In addition only subjects in the 7-11S, 7-11NS, 12-23S and 12-23NS groups were allowed to receive DTPw- HBV/Hib and OPV vaccines through the local EPI program. These vaccines were not considered as study vaccines.
- Other locally recommended vaccines (recommended through the EPI program or through national immunization campaigns), for example inactivated influenza vaccine, were always allowed, even if concomitantly administered with the study vaccines.

Blood samples were collected as follows:

- **<6 groups:** pre-vaccination, one month post-dose 3, pre-booster and one month post-booster.
- **7-11 groups:** pre-vaccination, one-month post-dose 2, pre-booster and one month post-booster.
- **12-23 groups:** pre-vaccination, prior to dose 2 and one month post-dose 2.

Note that an additional blood sample for SCD testing was to be taken at the pre-vaccination timepoint from subjects aged 7-11 and 12-23 months without haemoglobin status confirmed by electrophoresis available.

Study vaccines were to be given as follows:

- Subjects in the **<6 groups** were to receive 4 doses of 10Pn-PD-DiT vaccine co-administered with DTPw-HBV/Hib and OPV vaccines at 8, 12, 16 weeks and 9-10 months of age.
- Subjects in the **7-11 groups** were to receive 3 doses of 10Pn-PD-DiT vaccine starting at 7-11 months of age with an interval of at least 4 weeks (28-42 days) between primary doses. A booster dose was to be given with an interval of 2 to 4 months since the previous dose.

- Subjects in the **12-23 groups** were to receive 2 doses of 10Pn-PD-DiT vaccine starting at 12-23 months of age with an interval of 2 to 4 months between doses.

The 10Pn-PD-DiT vaccine was administered intramuscularly in the right thigh or deltoid (in children aged ≥ 12 months if the size of the deltoid muscle was adequate). The DTPw-HBV/Hib vaccine was administered IM in the left thigh and OPV was given orally.

Study population

Male or female infants between, and including, 8 weeks to 23 months of age at the time of the first vaccination and for whom the investigator believed that their parents/legally acceptable representative (LARs) could and would comply with the requirements of the protocol. Written informed consent was obtained from the parents/LARs of each subject.

Diagnosis and critera for inclusion

Additional inclusion criteria for children with SCD (<6S, 7-11S and 12-23S groups): subjects with diagnosis of SCD (homozygous SCD [haemoglobin SS disease], double heterozygous sickle haemoglobin C disease [haemoglobin SC disease] and the sickle β-thalassemias) and confirmed haemoglobin status by haemoglobin chromatography and electrophoresis (<6S group) or electrophoresis (7-11S and 12-23S groups). Subjects were to be free of any other known or suspected health problems that would contraindicate the initiation of routine immunizations outside a clinical trial context.

Additional inclusion criteria for healthy children (<6NS, 7-11NS and 12-23NS groups): Healthy subjects as established by medical history and clinical examination before entering into the study and with negative diagnosis of SCD and confirmed haemoglobin status by haemoglobin chromatography and/or electrophoresis.

Outcomes/endpoints

Primary endpoint:

- Evaluation of immune responses to components of the investigational vaccine, one month after primary vaccination (<6S and <6NS groups):
    - Concentrations of antibodies against vaccine pneumococcal serotypes.
    - Concentrations of antibodies against protein D.

Secondary endpoints:

Immunogenicity:

- Evaluation of the immune responses to components of the investigational vaccine, for additional parameters prior to and one month after primary vaccination (<6S, 7-11S, <6NS and 7-11NS groups):
    - Concentrations of antibodies against vaccine pneumococcal serotypes.
    - Opsonophagocytic activity against vaccine pneumococcal serotypes.
    - Concentrations of antibodies against vaccine-related pneumococcal serotypes 6A* and 19A.
    - Opsonophagocytic activity against vaccine-related pneumococcal serotypes 6A and 19A.
    - Concentrations of antibodies against protein D.
- Evaluation of the immune responses to components of the investigational vaccine, for additional parameters prior to and one month after booster dose (<6S, 7-11S, <6NS and 7-11NS groups):

- Concentrations of antibodies against vaccine pneumococcal serotypes.
- Opsonophagocytic activity against vaccine pneumococcal serotypes.
- Concentrations of antibodies against vaccine-related pneumococcal serotypes 6A* and 19A.
- Opsonophagocytic activity against vaccine-related pneumococcal serotypes 6A and 19A.
- Concentrations of antibodies against protein D.

- Evaluation of the immune responses to components of the investigational vaccine, prior to first dose, prior to and one month after second dose (12-23S and 12-23NS groups):
  - Concentrations of antibodies against vaccine pneumococcal serotypes.
  - Opsonophagocytic activity against vaccine pneumococcal serotypes.
  - Concentrations of antibodies against vaccine-related pneumococcal serotypes 6A* and 19A.
  - Opsonophagocytic activity against vaccine-related pneumococcal serotypes 6A and 19A.
  - Concentrations of antibodies against protein D.
- Evaluation of immune responses to some components of the co-administered DTPw-HBV/Hib vaccine, prior to and one month after primary vaccination, prior to, and one month after booster vaccination (<6S and <6NS groups):
  - Antibody concentrations against diphtheria toxoid, tetanus toxoid, *Bordetella pertussis* toxoid.

Safety and reactogenicity:

- Occurrence of each solicited adverse event (AE), within 4 days after each vaccine dose.
  - Local (any, grade 3) AEs.
  - General (any, grade 3, related) AEs.
- Occurrence of unsolicited AEs within 31 days after each vaccination.
- Occurrence of serious adverse events (SAEs) during the entire study period.

**Results of the antibody concentrations for the vaccine-related serotype 6A will be presented in a subsequent annex report when available.*

Statistical Methods

Analyses were performed as per Protocol Amendment 4, except for the vaccine-related serotypes 6A antibody concentrations results, since they were not available at time of this report.

Analysis of demographics

The analysis of demographics was performed separately for each epoch:

- Demographic characteristics (age at each vaccination in weeks or months, where appropriate, gender, height, weight and geographic ancestry) of each study cohort were tabulated.
- The mean age (plus range and standard deviation) of the enrolled subjects was calculated.

Analysis of immunogenicity

Within groups assessment

For each treatment group, at each timepoint that a blood sample result was available:

- Geometric Mean Concentrations/Titres (GMCs/GMTs) with 95% confidence intervals (CIs) were tabulated for each serotype/antigen.
- Seropositivity rates with exact 95% CIs were calculated for each appropriate serotype/antigen.
- Percentage of subjects with antibody concentrations ≥ 0.2 µg/mL was calculated for each pneumococcal serotypes (1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F).
- The distribution of antibody concentrations/titres for each serotype/antigen was displayed using tables and/or reverse cumulative distribution curves.

Analysis of safety

Descriptive analysis

- The percentage of subjects with at least one local symptom (solicited and unsolicited), with at least one general symptom (solicited and unsolicited) and with any symptom during the 31-day (Day 0-Day 30) follow-up period were tabulated with exact 95% CI after each vaccine dose and overall primary doses. The percentage of doses followed by at least one local symptom (solicited and unsolicited), by at least one general symptom (solicited and unsolicited) and by any symptom were tabulated, over the full (primary) vaccination course, with exact 95% CI. The same calculations were performed for symptoms rated as grade 3 and general symptoms with causal relationship to vaccination.
- The percentage of subjects reporting each individual solicited local and general symptom during the 4-day (Day 0-Day 3) solicited follow-up period were tabulated after each vaccine dose and overall (primary) doses, with exact 95% CI. The percentage of doses followed by each individual solicited local and general symptom were tabulated, over the full (primary) vaccination course, with exact 95% CI. The same tabulation was performed for grade 3 solicited symptoms and for solicited general symptoms with causal relationship to vaccination. For redness and swelling, grade 2 or 3 symptoms were also tabulated.
- Occurrence of fever was reported per 0.5°C cumulative increments.
- The proportion of subjects/doses with at least one report of unsolicited symptom classified by the Medical Dictionary for Regulatory Activities (MedDRA) and reported up to 30 days after (primary or booster) vaccination were tabulated with exact 95% CI. The same tabulation was performed for grade 3 unsolicited symptoms and for unsolicited symptoms with a relationship to vaccination.
- The proportion of symptoms resulting in a medically attended visit was also tabulated.
- The number and percentage of subjects who took concomitant antipyretic/medication at least once during the 4-day (Day 0-Day 3) solicited follow-up period were tabulated for each group after each vaccine dose and overall (primary) doses, with exact 95% CI. The number and percentage of doses for which the subjects took concomitant antipyretic/medication at least once during the 4-day (Day 0-Day 3) solicited follow-up period were tabulated over the full (primary) vaccination course, with exact 95% CI.
- SAEs, large swelling reactions (for children 9 months of age or above) and withdrawal due to AE(s) were described in detail.

Results

Recruitment/ Number analysed

A total of 300 subjects were enrolled in the study and received at least one dose of Synflorix; 50 subjects in each of the <6S, <6NS, 7-11S, 7-11NS, 12-23S and 12-23NS groups.

Baseline data

In the according-to-protocol (ATP) cohort for immunogenicity, the mean age at the time of the first visit (dose 1) was 8.5 weeks (SD ±0.9 weeks) in the <6 groups, 8.4 months (SD ±1.4 months) in the 7-11 groups and 16.6 months (SD ±3.4 months) in the 12-23 groups. All subjects in all groups were of African/African American heritage.

Efficacy results

Immunogenicity:

The primary analysis was performed on the according-to-protocol (ATP) cohort for immunogenicity.

One month following a 3-dose primary vaccination schedule (<6 groups)

- For each of the 10 vaccine serotypes:
  - At least 97.8% of subjects in both <6S and <6NS groups had antibody concentration ≥ 0.2 µg/mL, except for serotypes 6B (85.4% and 91.3%, respectively) and 23F (89.6% and 89.1%, respectively).
  - At least 93.2% and 89.7% of subjects in the <6S and <6NS groups, respectively, had OPA titre ≥ 8, except for serotypes 1 (77.8% and 75.6%, respectively), 6B (83.8% in the <6NS group) and 23F (81.8% and 83.8%, respectively).
- For vaccine-related serotype 19A, 58.3% and 62.2% of subjects in the <6S and <6NS groups, respectively, had antibody concentration ≥ 0.2 µg/mL . For vaccine-related serotype 6A, 38.1% and 19.5% of subjects in the <6S and <6NS groups, respectively, had OPA titre ≥ 8. For vaccine-related serotype 19A, these percentages were 28.9% and 8.8%, respectively.
- All subjects in both <6S and <6NS groups had anti-protein D antibody concentrations ≥ 100 EL.U/mL.
- All subjects in both <6S and <6NS groups had anti-DIPHT and anti-TET antibody concentrations ≥ 0.1 IU/mL and anti-BPT antibody concentration ≥ 15 EL.U/mL.

CHMP's comment:

The immunogenicity results for this age group are considered acceptable and rather similar among children with and without SCD.

Following a 2-dose primary vaccination schedule (7-11 groups)

- One month post-primary vaccination, for each of the 10 vaccine serotypes:
  - At least 98.0% and 93.9% of subjects in the 7-11S and 7-11NS groups, respectively, had antibody concentration ≥ 0.2 µg/mL, except for serotypes 6B (87.8% and 91.8%, respectively) and 23F (84.0% and 87.5%, respectively).

- At least 87.5% and 84.4% of subjects in the 7-11S and 7-11NS groups, respectively, had OPA titre ≥ 8.

- One month post-primary vaccination, for vaccine-related serotype 19A, 72.0% and 87.8% of subjects in the 7-11S and 7-11NS groups, respectively, had antibody concentration ≥ 0.2 µg/mL. For vaccine-related serotype 6A, 46.9% and 53.8% of subjects in the 7-11S and 7-11NS groups, respectively, had OPA titre ≥ 8. For vaccine-related serotype 19A, these percentages were 37.5% and 80.6%, respectively.
- One month post-primary vaccination course, all subjects in both 7-11S and 7-11NS groups had antiprotein D antibody concentrations ≥ 100 EL.U/mL.

CHMP's comment:

The immunogenicity results are in agreement with previous studies. The number of subjects with SCD reaching antibody concentration ≥ 0.2 µg/mL against vaccine serotypes and vaccine-related serotypes one month post-primary vaccination was comparable to the subjects without SCD. Also, the number of subjects with OPA titre ≥ 8 was rather similar among children with and without SCD.

Following a 2-dose catch-up vaccination schedule (12-23 groups)

- One month post-dose 2, for each of the 10 vaccine serotypes:
  - At least 91.7% and 93.5% of subjects in the 12-23S and 12-23NS groups, respectively, had antibody concentration ≥ 0.2 µg/mL.
  - At least 90.7% and 88.6% of subjects in the 12-23S and 12-23NS groups, respectively, had OPA titre ≥ 8, except for serotype 1 (79.1% in the 12-23NS group).
- One month post-dose 2, for vaccine-related serotype 19A, 95.8% and 97.8% of subjects in the 12-23S and 12-23NS groups, respectively, had antibody concentration ≥ 0.2 µg/mL. For vaccine-related serotype 6A, 70.0% and 66.7% of subjects in the 12-23S and 12-23NS groups, respectively, had OPA titre ≥ 8. For vaccine-related serotype 19A, these percentages were 84.2% and 91.3%, respectively.
- One month post-dose 2, all subjects in the 12-23S and 12-23NS groups (except one in the 12-23NS group) had anti-protein D antibody concentrations ≥ 100 EL.U/mL.

CHMP's comment:

The immunogenicity results are rather similar also in these age groups among children with and without SCD, regarding antibody levels towards the 10 vaccine serotypes, vaccine-related serotypes and protein D.

One month following booster vaccination

- For each of the 10 vaccine serotypes:
  - All subjects in the <6S and <6NS groups had antibody concentration ≥ 0.2 µg/mL, except for serotypes 14 (94.7% in the <6NS group) and 23F (97.7% and 94.7%, respectively). At least 93.9% and 93.8% of subjects in the 7-11S and 7-11NS groups, respectively, had antibody concentration ≥ 0.2 µg/mL.
  - At least 97.5%, 93.9%, 89.4% and 95.1% of subjects in the <6S, <6NS groups, 7-11S and 7- 11NS groups, respectively, had OPA titre ≥ 8.

- For vaccine-related serotype 19A, 84.1%, 78.4%, 89.8% and 95.8% of subjects in the <6S, <6NS, 7- 11S and 7-11NS groups, respectively, had antibody concentration ≥ 0.2 µg/mL. For vaccine-related serotype 6A, 47.4%, 40.6%, 60.0% and 62.8% of subjects in the <6S, <6NS, 7-11S and 7-11NS groups, respectively, had OPA titre ≥ 8. For vaccine-related serotype 19A, these percentages were 42.3%, 57.1%, 71.0% and 82.8%, respectively.
- All subjects in the <6S, <6NS, 7-11S and 7-11NS groups had anti-protein D antibody concentrations ≥ 100 EL.U/mL.
- All subjects in both <6S and <6NS groups had anti-DIPHT and anti-TET antibody concentrations ≥ 0.1 IU/mL and anti-BPT antibody concentration ≥ 15 EL.U/mL.

CHMP's comment:

The booster vaccination provides an acceptable antibody response among the age groups, both towards the vaccine serotypes, OPA, protein D and vaccine-related serotypes. The results were rather similar among children with and without SCD.

Synflorix seems to be immunogenic in children of 8 weeks age up to 2 years with or without SCD. The immune response did not seem to be influenced by SCD when Synflorix was given to infants at 8, 12 and 16 weeks with a booster dose at 9-10 months of age, and when given to children according to 2+1 or 2-dose catch-up schedules.

Safety/reactogenicity:

The primary analysis was performed on the Total Vaccinated Cohort (TVC).

Primary epoch (all groups)

Following a 3-dose primary vaccination schedule (<6 groups):

- **Any symptom:** during the 31-day post-vaccination period, at least one symptom (local or general; solicited or unsolicited) was reported following 80.0% and 76.7% of doses in the <6S and <6NS groups, respectively.
- **Solicited local symptoms:** during the 4-day post-vaccination period, pain was the most frequently reported solicited local symptom (reported after 12.7% and 16.7% of doses in the <6S and <6NS groups, respectively). No grade 3 solicited local symptoms were reported.
- **Solicited general symptoms:** during the 4-day post-vaccination period, fever was the most frequently reported solicited general symptom (reported after 69.3% and 60.7% of doses in the <6S and <6NS groups, respectively). Solicited general symptoms related to vaccination were reported after a maximum of 63.3% of doses (fever in the <6S group). No grade 3 solicited general symptoms were reported.

Following a 2-dose primary (7-11 groups) or a 2-dose catch-up (12-23 groups) vaccination schedule:

- **Any symptom:** during the 31-day post-vaccination period, at least one symptom (local and general; solicited and unsolicited) was reported following 70.0%, 68.0%, 59.0% and 68.0% of doses in the 7- 11S, 7-11NS, 12-23S and 12-23NS groups, respectively.
- **Solicited local symptoms:** during the 4-day post-vaccination period, pain was the most frequently reported solicited local symptom (reported after 12.0%, 17.0%, 14.0% and 9.2% of doses in the 7- 11S, 7-11NS, 12-23S and 12-23NS groups, respectively). No grade 3 solicited local symptoms were reported.

- **Solicited general symptoms:** during the 4-day post-vaccination period, fever was the most frequently reported solicited general symptom (reported after 44.0%, 37.0%, 33.0% and 27.6% of doses in the 7- 11S, 7-11NS, 12-23S and 12-23NS groups, respectively). Solicited general symptoms related to vaccination were reported after a maximum of 39.0% of doses (fever in the 7-11S group). No grade 3 solicited general symptoms were reported.

Unsolicited symptoms (all groups):

- During the 31-day post-vaccination period, the percentage of doses followed by at least one unsolicited symptom ranged from 28.6% (12-23NS group) to 48.0% (7-11NS group). At least one grade 3 unsolicited symptom was reported after one dose in each group, except for the <6S group.
- The percentage of doses followed by at least one unsolicited symptom with causal relationship to vaccination ranged from 1.0% (7-11NS group) to 3.3% (both <6 groups). No grade 3 unsolicited symptoms with causal relationship to vaccination were reported.

Booster vaccination (<6 and 7-11 groups)

- **Any symptom:** during the 31-day post-booster vaccination period, at least one symptom (local and general; solicited and unsolicited) was reported for 83.7%, 73.5%, 56.0% and 44.0% of subjects in the <6S, <6NS, 7-11S and 7-11NS groups, respectively.
- **Solicited local symptoms:** during the 4-day post-booster vaccination period, pain was the most frequently reported solicited local symptom (maximum incidence was 22.4% [<6S group]). No grade 3 solicited local symptom were reported.
- **Solicited general symptoms:** during the 4-day post-booster vaccination period, fever was the most frequently reported solicited general symptom (incidence ranged between 26.0% [7-11NS group] and 77.6% [<6S group]). Solicited general symptoms related to vaccination were reported for a maximum of 71.4% of subjects (fever in the <6S group). Grade 3 fever was reported for one subject in the <6NS group.
- **Unsolicited symptoms:** during the 31-day post-booster period, the percentage of subjects for whom at least one unsolicited symptom was reported ranged from 16.3% (<6S group) to 36.0% (7-11S group). One subject in the 7-11NS group was reported with one grade 3 unsolicited symptom. Five subjects (2 in each of the <6S and 7-11S groups and one in the 7-11NS group) reported one unsolicited symptom with causal relationship to vaccination. No grade 3 unsolicited symptom with causal relationship to vaccination were reported.

Serious adverse events (entire study period):

- 3 subjects died during this study, i.e. 2 subjects due to meningitidis salmonella and malnutrition, respectively, during the period between both epochs and one subject due to pyrexia during the booster epoch. These fatal SAEs were assessed by the investigator as not causally related to vaccination.
- At least one non-fatal SAE was reported for 7 subjects during the primary epoch, for 3 subjects during the booster epoch and for 12 subjects during the period between both epochs. All events recovered/resolved and were assessed by the investigator as not causally related to vaccination.

Withdrawals due to adverse events/serious adverse events: Three subjects were withdrawn due to fatal SAEs.

CHMP's comment:

Synflorix had an acceptable safety profile when administered in children with sickle-cell disease aged 8 weeks to 2 years and when co-administered with the other two vaccines included in the present study in children below 6 months of age.

No further regulatory actions are required.

2.2.3. Discussion on clinical aspects

The MAH has stated that the study 10PN-PD-DIT-064 (A phase III, open, controlled study to evaluate the immunogenicity, safety and reactogenicity of GSK Biologicals´10-valent pneumococcal conjugate vaccine administered to children with sickle-cell disease between 8 weeks and 2 years of age, as compared to healthy children) is part of a clinical development program.

In the present study, the results in subjects without SCD are in line with previous studies conducted in paediatric subjects. Moreover, the administration of Synflorix to subjects with SCD from 8 weeks to 23 months of age at the first vaccination showed an acceptable safety and immunogenicity profile for each of the vaccine serotypes and the vaccine-related serotype 19A.

The MAH proposes to submit a variation application to update the Synflorix SmPC with respect to the administration of Synflorix to subjects with sickle-cell disease. Based on the results provided with the present submission, the MAH is encouraged to submit such a variation application.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

This article 46 submission is considered satisfactory and no further regulatory action regarding *Synflorix* is required.

Recommendation

☒ **Fulfilled**