22 June 2017
EMA/345979/2017 Corr.1
Committee for Medicinal Products for Human use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Bexsero

meningococcal group b vaccine (rdna, component, adsorbed)

Procedure no: EMEA/H/C/002333/P46/024

Note

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

[1] 25 October 2017

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Table of contents

1. Introduction

On April 6, 2017, the MAH submitted a completed paediatric study for Bexsero, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study V72_60 "A Phase 3, Open Label, Randomized, Controlled, Multi- Center Study to Evaluate the Safety and Immunogenicity of Novartis Meningococcal B Recombinant Vaccine When Administered concomitantly with Routine Vaccines to Healthy Infants in Taiwan" is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The commercially available formulation was used in the study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study V72_60 A Phase 3, Open Label, Randomized, Controlled, Multi- Center Study to Evaluate the Safety and Immunogenicity of Novartis Meningococcal B Recombinant Vaccine When Administered concomitantly with Routine Vaccines to Healthy Infants in Taiwan

2.3.2. Clinical study

A Phase 3, Open Label, Randomized, Controlled, Multi- Center Study to Evaluate the Safety and Immunogenicity of Novartis Meningococcal B Recombinant Vaccine When Administered concomitantly with Routine Vaccines to Healthy Infants in Taiwan

Methods

Objective(s)

Immunogenicity Objectives

Primary Immunogenicity Objective

To demonstrate the sufficiency of the immune response to rMenB+OMV NZ vaccine, when given concomitantly with routine vaccines (ie, DTaP-IPV-Hib, HepB and PCV-13) to healthy infants at 2, 4, 6 months of age, as measured by percentage of subjects with serum bactericidal activity (SBA) titer ≥ 1:5 against the indicator strains H44/76, 5/99 and NZ98/254 at 1 month after the third vaccination (at 7 months of age).

Key Secondary Immunogenicity Objective

To demonstrate the sufficiency of the immune response to a booster dose of rMenB+OMV NZ vaccine when given concomitantly with routine vaccines (i.e., MMR and varicella) to healthy toddlers at 12 months of age that were previously primed with 3-doses of rMenB+OMV NZ, as measured by percentage of subjects with SBA titer ≥ 1:5 against the indicator strains H44/76, 5/99 and NZ98/254 at 1 month after the booster dose (at 13 months of age).

Other Secondary Immunogenicity Objective

To assess bactericidal antibodies against meningococcal B in healthy infants receiving rMenB+OMV NZ concomitantly with routine vaccines (Group A2) or routine vaccines alone (Group B2) at 2, 4, 6 and 12 months of age, as measured by SBA geometric mean titers (GMTs), geometric mean ratios between post and pre-vaccination (baseline) titers (GMRs) and percentage of subjects with SBA titer ≥ 1:5 against indicator strains H44/76, 5/99, NZ98/254 and strain M10713 at baseline (2 months of age), 1 month after the third vaccination (7 months of age), prior to the booster dose (12 months of age) and at 1 month after the booster dose (13 months of age).

Safety Objectives

To assess the safety and tolerability of 3 doses of rMenB+OMV NZ given at 2, 4, 6 months of age, followed by a booster dose at 12 months of age when concomitantly administered with routine vaccines (ie, combined DTaP-IPV-Hib and PCV-13 at 2, 4, 6 months; HepB at 6 months of age; MMR and varicella at 12 months of age) and of routine vaccines alone in terms of percentages and numbers of subjects with:

- Solicited local and systemic adverse events (AEs) reported from day 1 (day of vaccination) through day 7 after each vaccination. (Fever, rash and parotid/salivary gland swelling will be collected for an extended period of 28 days after MMR and varicella vaccination);
- Any unsolicited AEs reported from day 1 through day 7 after each vaccination;
- Serious adverse events (SAEs), medically attended AEs, AEs leading to withdrawal from the study throughout the entire study.

Study design

This was a phase 3, randomized, controlled, open-label, multicenter study in healthy infants aged approximately 2 months at the time of enrollment.

Study population /Sample size

Number of Subjects (planned and analyzed): To obtain 120 evaluable subjects, it was estimated that approximately 150 eligible subjects would be needed to be enrolled in the rMenB+Routine group, to allow for a dropout rate of approximately 20%. Taking into account a randomization ratio between rMenB+Routine: Routine of 2:1, 75 eligible subjects were needed to be enrolled in the Routine group. The number of subjects planned to be enrolled and actually enrolled are listed in Table 2-1.

Table 2-1 Randomization Groups and Visit Schedule

Group	Number of Subjects									
	Planned	Enrolled	2 months (Visit 1)	4 months (Visit 2)	6 months (Visit 3)	7 months (Visit 4)	9 months (Visit 5)	11 months (Visit 6)	12 months (Visit 7)	13 months (Visit 8)
rMenB + Routine	150	150	**rMenB+OMV NZ** DTaP-IPV-Hib Pneumococcal (PCV-13) Blood Draw	**rMenB+OMV NZ** DTaP-IPV-Hib Pneumococcal (PCV-13)	**rMenB+OMV NZ** DTaP-IPV-Hib Pneumococcal (PCV-13) HepB (3rd dose)*	Blood Draw	Safety Call	Safety Call	**rMenB+OMV NZ** MMR Varicella Blood Draw	Blood Draw
Routine	75	75	DTaP-IPV-Hib Pneumococcal (PCV-13) Blood Draw	DTaP-IPV-Hib Pneumococcal (PCV-13)	DTaP-IPV-Hib Pneumococcal (PCV-13) HepB (3rd dose)*	Blood Draw	Safety Call	Safety Call	MMR Varicella Blood Draw	Blood Draw

Diagnosis and Main Criteria for Inclusion and Exclusion:

Healthy male and female infants approximately 2 months of age.

Treatments

The rMenB+OMV NZ vaccine was administered in a 3-dose schedule (at 2, 4 and 6 months of age), followed by a booster at 12 months age. Concomitantly, infants received routine vaccines (ie, diphtheria [D], tetanus [T], acellular pertussis [aP], poliovirus types 1, 2, 3 [IPV], Hepatitis B [HepB], *Haemophilus influenzae* type b [Hib], 13-valent pneumococcal conjugate vaccine [PCV-13], measles, mumps, rubella [MMR] and varicella). For safety comparison and to assess the prevalence of bactericidal meningococcal B antibodies over the study period in those infants not receiving rMenB+OMV NZ vaccine, these infants received routine vaccines alone as a control.

Prior to the first vaccination (at 2 months of age), 1 month after the third vaccination (at 7 months of age), prior to the booster vaccination (at 12 months of age) and 1 month after the booster vaccination (at 13 months of age) a blood sample was taken from all subjects to evaluate bactericidal antibodies against meningococcal B. Vaccinations and blood samples were completed according to Table 2-1.

Outcomes/endpoints

Immunogenicity Endpoints

Primary

The percentage of subjects with human serum bactericidal activity (hSBA) titer ≥ 5 at 1 month following the third vaccination (at 7 months of age) against the indicator strains H44/76, 5/99 and NZ98/254.

Key Secondary

The percentage of subjects with hSBA titer ≥ 5 at 1 month following the booster vaccination (13 months of age) against the indicator strains H44/76, 5/99 and NZ98/254.

Other Secondary

The hSBA GMTs, GMRs and percentage of subjects with hSBA titer ≥ 5 against the indicator strains H44/76, 5/99, NZ98/254 and strain M10713 at baseline (2 months of age), 1 month after the third

vaccination (7 months of age), prior to the booster dose (12 months of age) and at 1 month after the booster dose (13 months of age).

Other Endpoints

The percentage of subjects with hSBA titers ≥ 8 at baseline, one month after the third vaccination, at 12 months of age (prior to the booster dose) and at 13 months of age (one month after the booster dose) for each of the three indicator strains (H44/76, 5/99, NZ98/254) and strain M10713.

Safety Endpoints

Local (ie, injection site erythema, induration, tenderness and swelling) and systemic (ie, change in eating habits, sleepiness, irritability, persistent crying, vomiting, diarrhea, rash, fever [temperature ≥ 38.0 ° C] and medically attended fever) AEs were assessed for 7 days (including the day of vaccination) after each vaccination.

All AEs occurring during the 7 days (including the day of vaccination) after each vaccination were collected on a diary card.

SAEs, medically attended AEs and AEs that result in a subject's withdrawal from the study were collected throughout the entire study period.

After the administration of MMR and varicella vaccines (with and without rMenB+OMV NZ) at 12 months of age, rash, parotid/salivary gland swelling, fever (temperature ≥38.0° C), medically attended fever and use of antipyretic medication were assessed for a prolonged period up to day 28 following MMR and Varicella vaccination.

Statistical Methods

The percentage of subjects with hSBA titer ≥ 5 were presented as point estimates along with the associated 95% Clopper-Pearson confidence intervals (CIs) at baseline (2 months of age, visit 1), 1 month after the third injection (7 months of age, visit 4), prior to the booster dose (12 months of age, visit 7) and at 1 month after the booster dose (13 months of age, visit 8) for the meningococcal B indicator strains H44/76, 5/99 and NZ98/254.

The criterion for the primary objective for a sufficient immune response at visit 4 (ie, 1 month after the third injection) was that the lower limit of the two-sided 95% CI for the percentage of subjects with hSBA titer ≥ 5 should be > 70%.

The criterion for the secondary objective for a sufficient immune response at visit 8 (1 month after booster) was that the lower limit of the two-sided 95% CI for the percentage of subjects with hSBA titer ≥ 5 was > 75%.

In addition, for each strain (H44/76, 5/99, NZ98/254 and M10713) the GMTs at baseline, at 7 months of age, at 12 month of age and at 13 month of age and the post-vaccination to pre-vaccination (baseline) GMR and their associated 95% CIs median, minimum and maximum antibody titers were determined using descriptive statistics and presented together with number of subjects for each vaccine group.

All statistical analyses were performed on the logarithmically (base 10) transformed titers or concentrations.

Results

Recruitment / Number analysed

A total of 225 subjects were enrolled into the study and randomized to the 2 treatment groups. Among 150 enrolled subjects in rMenB+Routine group, 148 subjects were exposed to at least one dose of the rMenB+OMV NZ vaccine. In the Routine group, 73 out of 75 enrolled subjects received at least one of the routine vaccinations. Overall, 98% of subjects met all inclusion criteria. The demographic and baseline characteristics were well-balanced across the study groups.

Immunogenicity results

Primary Objective

Percentages of subjects with hSBA titers ≥ 5 against N meningitidis serogroup B strains H44/76, 5/99 and NZ98/254 at 1 month following the third vaccination:

In the rMenB+Routine group, at 1 month following the third vaccination, hSBA titers ≥ 5 were achieved in all subjects against strains H44/76 and 5/99, and in 79% of subjects against strain NZ98/254. The lower limits of the 2-sided 95% CI for the percentage of subjects with hSBA titers ≥ 5 were 97.2% for H44/76 and 5/99, and 71.4% for NZ98/254 strain, all above the pre-specified sufficient immune response margin set at >70% (Table 11.4.1-1).

Therefore, the primary objective to demonstrate the sufficiency of the immune response to rMenB+OMV NZ vaccine, when given concomitantly with routine vaccines (ie, DTaPIPV-Hib, HepB and PCV-13) to healthy infants at 1 month after the third vaccination (at 7 months of age) was met

Table 11.4.1-1 Numbers (%) (95% CI) of Subjects with hSBA Titer ≥ 5 at Baseline and 1 Month After Third Vaccination, by Strain – FAS-1

Vaccine Group	rMenB+Routine	Routine
H44/76 (fHbp)	**N = 130**	**N = 66**
Baseline	0 (0%) (0% - 3.1%) N = 116	0 (0%) (0% - 6.1%) N = 59
One month after third vaccination	130 (100%) (**97.2**% – 100%)	0 (0%) (0% – 5.4%)
5/99 (NadA)	**N = 129**	**N = 70**
Baseline	1 (1%) (0.02% - 4.4%) N = 124	1 (1%) (0.04% – 7.8%) N = 69
One month after third vaccination	129 (100%) (**97.2**% - 100%)	0 (0%) (0% - 5.1%)
NZ98/254 (PorA P1.4)	**N = 135**	**N = 71**
Baseline	0 (0%) (0% - 2.7%) N = 134	0 (0%) (0% - 5.1%)
One month after third vaccination	107 (79%) (**71.4**% - 85.8%)	0 (0%) (0% - 5.1%)
M10713 (NHBA)	**N = 123**	**N = 65**
Baseline	10 (10%) (4.9% - 17.6%) N = 100	11 (19%) (10% - 31.9%) N = 57
One month after third vaccination	73 (59%) (50.1% - 68.1%)	5 (8%) (2.5% - 17%)

Key Secondary Objective

***Percentages of subjects with hSBA titers ≥ 5 against N meningitidis serogroup B strains H44/76, 5/99 and NZ98/254 at 1 month after booster vaccination**:*

In the rMenB+Routine group, before the booster vaccination (at 12 months of age), 81%, 99% and 17% of subjects had hSBA titers ≥ 5 against strains H44/76, 5/99 and NZ98/254, respectively. At 1 month following the booster vaccination, hSBA titers ≥ 5 were achieved in 99% of subjects against strain H44/76 and 5/99, and in 94% of subjects against NZ98/254 (Table 11.4.1-3).

Although not part of the sufficiency analyses, the percentage of subjects with hSBA titers ≥ 5 were also evaluated against strain M10713. Prior to booster vaccination in the rMenB+Routine group, 22% of subjects had titers ≥ 5 which increased to 92% at one month following booster vaccination (Table 11.4.1-3).

Table 11.4.1-3 Numbers (%) (95% CI) of Subjects with hSBA Titers ≥5 Before Booster Vaccination and 1 Month After Booster Vaccination, by Strain – FAS-3

Vaccine Group	rMenB+Routine	Routine
H44/76 (fHbp)	**N = 127**	**N = 64**
Before booster	100 (81%) (73.3% - 87.8% N = 123	1 (2%) (0.04% - 8.4%)
One month after booster	126 (99%) (**95.7**% - 99.98%)	1 (2%) (0.04% - 8.4%)
5/99 (NadA)	**N = 135**	**N = 71**
Before booster	133 (99%) (94.8% - 99.82%)	1 (1%) (0.04% – 7.7%) N = 70
One month after booster	132 (99%) (**94.7**% - 99.82%) N = 134	0 (0%) (0% - 5.1%)
NZ98/254 (PorA P1.4)	**N = 136**	**N = 71**
Before booster	23 (17%) (11.0% - 24.3%)	1 (1%) (0.04%-7.7%) N = 70
One month after booster	128 (94%) (**88.7**% - 97.4%)	0 (0%) (0% - 5.1%)
M10713 (NHBA)	**N = 130**	**N = 69**
Before booster	28 (22%) (14.8% - 29.6%)	7 (11%) (4.4% - 20.9%) N = 65
One month after booster	120 (92%) (86.3% - 96.2%)	9 (13%) (6.1% - 23.3%)

Other Secondary Objectives

GMTs and GMRs at baseline, after third vaccination (7 months of age), before booster vaccination (12 months of age) and following booster vaccination (13 months of age):

In the rMenB+Routine group, hSBA GMTs were low at baseline against all serogroup B indicator strains. At one month following the third vaccination, antibody levels had increased against all strains (H44/76: 72, 5/99: 963, NZ98/254: 9.20, M10713: 8.41).

The GMRs following the third vaccination with respect to the baseline were 71, 875, 9.18 and 5.69 against strains H44/76, 5/99, NZ98/254 and M10713, respectively.

At 12 months of age, before the booster dose, hSBA GMTs were higher than at baseline, although lower than one month after the third vaccination for all 4 strains (H44/76: 11, 5/99: 205, NZ98/254: 1.91, M10713: 2.18).

The hSBA GMTs increased following booster vaccination against all 4 strains (H44/76: 157, 5/99: 2315, NZ98/254: 26, M10713: 17). The GMRs with regard to baseline values were 155 for H44/76, 2110 for 5/99, 25 for NZ98/254 and 12 for M10713.

In the Routine group, hSBA GMTs were low at baseline against all serogroup B indicator strains. There was no increase in GMTs against any strain in Routine group at 12 or 13 months of age, as expected.

Safety results

All enrolled subjects except two in each study group were exposed to at least one dose of the study vaccines. Overall ≥ 93% of exposed subjects in each study group were included in both solicited and unsolicited safety sets.

Solicited AEs:

- Overall after any vaccination, at least one solicited AE was experienced by all subjects in rMenB+Routine group and by 93% subjects in the Routine group (Table 2-7).
- After any vaccination, the percentages of subjects experiencing at least one solicited local AE and solicited systemic AEs were higher in rMenB+Routine group than in Routine group (solicited local AEs: 89% vs. 71%, solicited systemic AEs: 100% vs. 89%). A similar trend was observed after each individual vaccination, with percentages decreasing for each group following subsequent vaccinations (Table 2-7).

Solicited local AEs:

After each vaccination of rMenB+OMV NZ:

- After each vaccination in the rMenB+Routine group, the most frequently reported solicited local AE was injection site tenderness in ≤ 51% of subjects, and was the only solicited local AE reported as a severe in intensity (≤ 5% subjects).
- For the majority of subjects in the rMenB+Routine group, the first onset of solicited local AEs was from 30 minutes through day 2 after each vaccination.

After each routine vaccination (PCV-13, DTaP-IPV-Hib, Hepatitis B, MMR, and Varicella):

- After each of the routine vaccinations, the most frequently reported solicited local AE in the rMenB+Routine group was injection site tenderness (PCV-13: ≤ 34%, DTaPIPV-Hib: ≤ 32%, Hepatitis B: 33%, MMR: 27%, Varicella: 30%).
- In the Routine group, the most frequently reported solicited local AEs were injection site induration (PCV-13: ≤ 21%, DTaP-IPV-Hib: ≤ 22%, Hepatitis B: 24%) and erythema (MMR: 18%, Varicella: 19%).
- After each routine vaccination, injection site tenderness was the only solicited local AE reported as severe, by ≤2% of subjects in the rMenB+Routine group.

Solicited systemic AEs:

After any vaccination (from day 1 through 7 following vaccination):

- The most frequently reported solicited systemic AEs after every vaccination in both rMenB+Routine and Routine groups were irritability (rMenB+Routine group: ranged from 75% to 52%, Routine group: ranged from 44% to 22%.
- After each vaccination in rMenB+Routine group, fever (temperature ≥ 38°C) was reported by higher percentage of subjects (51% to 44%) than in Routine group (15% to 8%. Severe fever (temperature ≥ 40°C) was reported by one subject in rMenB+Routine group after second vaccination, and by one in each group after booster vaccination.

- Majority of solicited systemic AEs after each vaccination were mild to moderate in intensity.

After MMR/Varicella vaccination at 12 months of age (from day 1 through 28 following vaccination):

- In both rMenB+Routine and Routine groups, a similar percentage of subjects reported lymphadenopathy (parotid / salivary gland swelling: 25% and 29% respectively) and rash (36% and 33%). Severe rash was reported in 4% and 7% of subjects, respectively.
- A higher percentage of subjects (66%) in rMenB+Routine group reported fever (temperature ≥ 38°C) than in Routine group (46%; Table 12.2.3-8). Only 1% subjects in rMenB+Routine group and 7% subjects in Routine group reported severe fever (temperature ≥ 40°C)

Unsolicited AEs:

From day 1 up to day 7 after any vaccination:

Overall, the percentages of subjects experiencing unsolicited AE from day 1 up to day 7 after any vaccination were 72% in the rMenB+Routine group and 42% in the Routine group

The most frequently reported unsolicited system organ class (SOC) of AEs from day 1 up to day 7 after any vaccination was 'general disorders and administration site conditions' (rMenB+Routine group: 58%, Routine group: 21%).

The most frequently occurring unsolicited AEs by preferred term reported from day 1 up to day 7 after any vaccination was injection site induration (rMenB+Routine: 52%, Routine: 17%.

The percentages of subjects reporting at least possibly or probably related unsolicited AEs from day 1 up to day 7 after any vaccination were 59% in the rMenB+Routine group and 24% in Routine group. These were due to solicited AEs that were ongoing after the 7 day reporting period.

The most frequently occurring possibly or probably related AE by preferred term reported from day 1 up to day 7 after any vaccination was injection site induration (rMenB+Routine group: 51%, Routine group: 14%.

From day 1 up to day 335 after any vaccination:

The percentages of subjects reporting medically attended AEs from day 1 to day 335 were similar in rMenB+Routine group and Routine groups (90% versus 92%).

A single subject in rMenB+Routine group reported unsolicited AEs (congenital cystic kidney and renal dysplasia) that led to premature withdrawal from the study.

SAEs were reported by 13 subjects in rMenB+Routine group and by 8 subjects in the Routine group. None of the SAEs were considered by the investigator to be possibly related to the study vaccine and all were resolved prior to study completion. No death occurred in the study.

Table 2-7 Numbers (%) of Subjects with Solicited Local and Systemic AEs and Other Solicited Data for 7 Days After Each Vaccination –Solicited Safety Set

Vaccine Group	rMenB+Routine	Routine
Any Vaccination	**N = 148**	**N = 73**
Any[a]	148 (100%)	68 (93%)
Local	131 (89%)	52 (71%)
Systemic	148 (100%)	65 (89%)
First Vaccination	**N = 148**	**N = 73**
Any[a]	141 (95%)	58 (79%)
Local	107 (72%)	30 (41%)
Systemic	140 (95%)	54 (74%)
Second Vaccination	**N = 140**	**N = 72**
Any[a]	128 (91%)	55 (76%)
Local	92 (66%)	29 (40%)
Systemic	120 (86%)	48 (67%)
Third Vaccination	**N = 138**	**N = 72**
Any[a]	124 (90%)	53 (74%)
Local	99 (72%)	34 (47%)
Systemic	116 (84%)	39 (54%)
Booster Vaccination	**N = 137**	**N = 72**
Any[a]	121 (88%)	40 (56%)
Local	91 (66%)	17 (24%)
Systemic	116 (85%)	33 (46%)

2.3.3. Discussion on clinical aspects

The aim of the study was to evaluate the safety and immunogenicity of rMenB+OMV NZ vaccine when administered concomitantly with routine vaccines to healthy infants in Taiwan. The immunogenicity results were in agreement with other previously reported studies in infants and toddlers from other parts of the world.

The safety results were also in agreement with previously reported clinical studies in the same age groups, and no new safety signal was detected in this study.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

The results of this study show that the immune responses were well in agreement with previous studies, and no new safety signal was detected. Thus, this paediatric procedure is considered fulfilled and no further regulatory action is required based on this study.

Recommendation

☒ **Fulfilled:**

No regulatory action required.

4. Additional clarifications requested

Not applicable.