Safety, Tolerability, and Immunogenicity of an Investigational Meningococcal Serogroup B Bivalent rLP2086 Vaccine When Administered in Regimens of 2 or 3 Doses in Healthy Adolescent Subjects aged 11 to 18 Years

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INTRODUCTION

- *Neisseria meningitidis* serogroup B (MnB) causes most meningococcal disease in England and Wales.[1]
  - Polysaccharide vaccines developed against MnB disease are poorly immunogenic. Thus, alternative protein-based MnB antigens have been investigated as vaccine candidates.
- LP2086 is a factor H binding protein (fHBP), an important meningococcal virulence factor.
  - Conserved surface-exposed bacterial lipoprotein that binds human factor H[2]
  - The LP2086 gene is present in all isolates in a comprehensive survey of 1837 invasive MnB strains.
    - 2 genetically distinct subfamilies: A (30% of isolates) and B (70%)[3]
- A bivalent rLP2086 vaccine containing one recombinant lipidated protein variant from each subfamily is currently in phase 3 clinical development.
  - In phase 1 and 2 studies, sera from vaccinees demonstrated killing activity, as measured in the serum bactericidal assay using human complement (hSBA), against MnB strains bearing fHBP variants heterologous to those in the vaccine.[4,7]
  - Based on the immunogenicity and tolerability demonstrated in a phase 2 study in adolescents, the 120-µg dose was selected for further clinical development.[6]

OBJECTIVE

- This study assessed safety and immunogenicity of 2 or 3 doses of bivalent rLP2086 in healthy adolescents 11–18 years of age.

METHODS

Study Design

- Phase 2, multicenter, randomized, placebo-controlled, single-blind study conducted in the Czech Republic, Denmark, Germany, Poland, Spain, and Sweden.
- Subjects were randomized (3:3:3:2:1, corresponding to group 1: group 2: group 3: group 4: group 5) and stratified by age (≥11–<14 and ≥14–<19 y).
- Subjects attended vaccination visits at months 0, 1, 2 and 6, at which they received 1 intramuscular (IM) dose of the bivalent rLP2086 vaccine or saline.
  - Each 0.5-mL, 120-µg dose of bivalent rLP2086 contained 60 µg rLP2086 from each of the A (A05) and B (B01) subfamilies produced in *E coli* and formulated with aluminium phosphate in an isotonic buffer in pre-filled syringes.
  - Blood samples for hSBA were obtained at months 0, 2, 3, and 7 **(Table 1)**.

Table 1. Study Design

	Visit 1* (Month 0)	Visit 2 (Month 1)	Visit 3* (Month 2)	Visit 4* (Month 3)	Visit 5 (Month 6)	Visit 6* (Month 7)	Visit 7 (Month 12)
Group (rLP2086, mo)	Injection 1	Injection 2	Injection 3	Blood Draw Only	Injection 4	Blood Draw Only	Telephone Contact Only
1 (0, 1, 6)	rLP2086	rLP2086	Saline		rLP2086		
2 (0, 2, 6)	rLP2086	Saline	rLP2086		rLP2086		
3 (0, 6)	rLP2086	Saline	Saline		rLP2086		
4 (0, 2)	rLP2086	Saline	rLP2086		Saline		
5 (2, 6)	Saline	Saline	rLP2086		rLP2086		

*Blood draw at visits 1, 3, 4, 6 for hSBA performed with strains expressing fHBP variants A22, A56, B24, and B44.

Key Inclusion and Exclusion Criteria

- Inclusion criteria
  - Healthy adolescent, ≥11–<19 years of age at the time of enrollment
  - Written informed consent and willingness to comply with study procedures
  - Not pregnant or breastfeeding; willing to practice an effective form of contraception during the trial
- Key exclusion criteria
  - Previous vaccination with any MnB vaccine
  - A previous anaphylactic reaction to any vaccine or vaccine-related component
  - History of culture-proven *N meningitidis* or *N gonorrhoeae* disease
  - Current chronic use of systemic antibiotics
  - Bleeding diathesis or condition associated with prolonged bleeding time that would contraindicate IM injection
  - Known or suspected disease of the immune system or receipt of immunosuppressive therapy; significant neurologic disorder or history of seizure (excluding simple febrile seizure); or any neuroinflammatory or autoimmune condition, including, but not limited to, transverse myelitis, uveitis, optic neuritis, and multiple sclerosis
  - Receipt of any blood products, including immunoglobulin, within 6 months of the first study vaccination

Safety Assessments

- Collected by electronic diary (e-diary) for 7 days after each injection
  - Reactogenicity: solicited local reactions and systemic events
  - Use of antipyretic medications
  - Unsolicited adverse events (AEs): severity, relationship to study drug, seriousness, outcome
  - The subject/guardian of those who experienced autoimmune diseases provided written consent to perform additional testing to evaluate the disease at baseline.

Immunogenicity

- Functional bactericidal antibodies were assessed in hSBA assays using 4 MnB test strains expressing LP2086 variants that are heterologous to those in the vaccine; 2 expressing subfamily A (A22 and A56) and 2 expressing subfamily B (B24 and B44).
  - Variants B24 and B44 are important epidemiologically for the United States and Europe, including the United Kingdom.[3]
  - Variant A22 is the most common variant of subfamily A in the United States and Europe.[3]
- Efficacy endpoints: proportion of subjects achieving an hSBA titer ≥1:8 for each of the 4 MnB test strains at 1 month after the third dose in groups 1 and 2 (primary endpoint) and 1 month after the second dose in group 3 (secondary endpoint)
  - Response rate compared with 50% at a significance level of 1.25%, using a 1-sided exact test based on binomial distribution
  - Primary immunogenicity objective achieved if $P<0.0125$ for each of the 4 MnB test strains in *either* group 1 or 2

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RESULTS

Subjects

- A total of 1712 subjects, 51% female, were vaccinated **(Table 2)**.
  - Most were white (99%) and non-Hispanic (99%).
  - Mean age was 14 years.

Table 2. Subject Demographics

	Group 1 0, 1, 6 mo (n=426)	Group 2 0, 2, 6 mo (n=414)	Group 3 0, 6 mo (n=451)	Group 4 0, 2 mo (n=277)	Group 5 2, 6 mo (n=144)	Total (N=1712)
Sex, n (%)						
Female	212 (50)	217 (52)	227 (50)	135 (49)	79 (55)	870 (51)
Race, n (%)						
White	423 (99)	408 (99)	448 (99)	272 (98)	144 (100)	1695 (99)
Age, y						
Stratified, n (%)						
11–<14	155 (36.4)	154 (37.2)	164 (36.4)	101 (36.5)	53 (36.8)	627 (36.6)
14–<19	271 (63.6)	260 (62.8)	287 (63.6)	176 (63.5)	91 (63.2)	1085 (63.4)
Mean (SD)	14.4 (2.22)	14.4 (2.23)	14.4 (2.17)	14.4 (2.25)	14.3 (2.11)	14.4 (2.20)
Median	14	15	14	14	14	14
Range	11, 18	11, 18	11, 18	11, 18	11, 18	11, 18

Safety

- Reactogenicity
  - Local reactions were generally most frequent after dose 1 of rLP2086 **(Figure 1)**.
  - Fever ≥38°C was reported in 3.3%–6.5% of subjects across the groups after the first dose of rLP2086 compared with 2.1% in those receiving a first dose of saline **(Figure 2)**.

Figure 1. Local, Injection Site Reactogenicity (Recorded by E-diary)

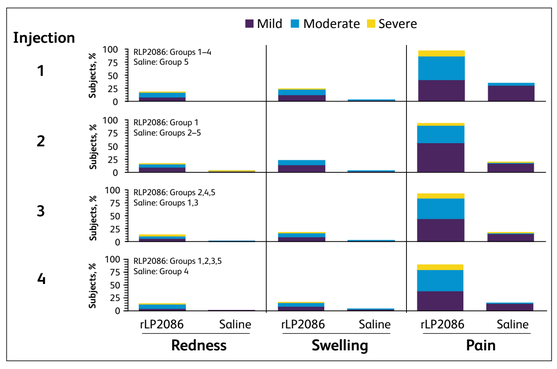
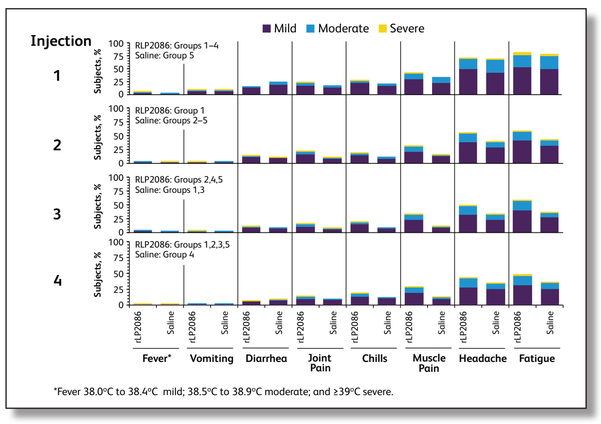


Figure 2. Systemic Reactogenicity (Recorded by E-diary)



- Median duration ranged from 1.0–3.5 days.
  - Antipyretic medication was used by 14%–16% of subjects after a dose of rLP2086 and by 8%–9% of subjects after a saline dose.
- Unsolicited AEs
  - 43 of 1712 subjects (2.5%) reported 51 serious AEs; 2 cases were considered related to treatment (1 case of vertigo, chills, and headache and 1 case of fever and vomiting).
  - Autoimmune diseases were diagnosed in 5 subjects.
    - Diagnoses included hypothyroidism (n=2), Graves-Basedow disease (n=1), Crohn's disease (n=1), and rheumatoid arthritis (n=1).
    - Assessment of baseline serum samples for auto-antibodies and past medical history indicates that the autoimmune diseases were undiagnosed preexisting conditions.
  - No neuroinflammatory SAEs were reported.
  - No deaths were reported.

Immunogenicity

- 1 month after the last vaccine dose, 86%–99% subjects (after 3 doses; $P<0.001$) and 69%–100% of subjects (after 2 doses) had hSBA titers ≥1:8 to 4 MnB test strains expressing LP2086 variants heterologous to those included in the bivalent vaccine **(Table 3)**.
  - Prevaccination rates were 5%–28% in the 3-dose groups and 4%–25% in the 2-dose groups.

Table 3. Percentage of Subjects with hSBA Titer ≥1:8 One Month after Receipt of Full Vaccination Regimen*

		Group 1 (0, 1, 6 mo) % (95% CI)†	Group 2 (0, 2, 6 mo) % (95% CI)†	Group 3 (0, 6 mo) % (95% CI)†	Group 4 (0, 2 mo) % (95% CI)†	Group 5 (2, 6 mo) % (95% CI)†
PMB80 [A22]	Prevaccination	28.1 (23.5, 33.1)	21.9 (17.7, 26.6)	24.7 (20.4, 29.5)	22.6 (17.4, 28.4)	25.0 (17.2, 34.3)
	Postvaccination	91.7 (88.3, 94.3)‡	95.0 (92.1, 97.0)‡	93.5 (90.5, 95.8)‡	90.8 (86.3, 94.1)	91.9 (85.2, 96.2)
PMB2001 [A56]	Prevaccination	20.9 (16.7, 25.5)	18.7 (14.7, 23.2)	21.7 (17.5, 26.3)	19.0 (14.2, 24.7)	17.8 (11.0, 26.3)
	Postvaccination	99.4 (98.0, 99.9)‡	98.9 (97.2, 99.7)‡	98.4 (96.5, 99.4)‡	100.0 (98.5, 100.0)	99.1 (95.2, 100.0)
PMB2948 [B24]	Prevaccination	16.3 (12.6, 20.5)	13.8 (10.4, 17.8)	13.0 (9.7, 16.9)	11.2 (7.5, 15.9)	14.3 (8.4, 22.2)
	Postvaccination	89.0 (85.2, 92.0)‡	88.4 (84.6, 91.6)‡	81.1 (76.6, 85.0)‡	73.0 (66.9, 78.5)	69.1 (59.6, 77.6)
PMB2707 [B44]	Prevaccination	5.2 (3.2, 8.1)	6.2 (3.9, 9.2)	6.2 (4.0, 9.2)	7.5 (4.5, 11.5)	4.4 (1.5, 10.0)
	Postvaccination	88.5 (84.7, 91.6)‡	86.1 (82.0, 89.5)‡	77.5 (72.8, 81.8)‡	70.1 (63.8, 75.9)	73.0 (63.7, 81.0)

hSBA=human serum bactericidal activity.
*After second or third rLP2086 dose for 2- or 3-dose groups, respectively.
†Exact 2-sided confidence interval (Clopper and Pearson) based upon the observed proportion of subjects.
‡$P<0.001$ compared with 50%, using 1-sided exact test based on binomial distribution.

CONCLUSIONS

- The investigational bivalent rLP2086 vaccine was generally well tolerated, including acceptable reactogenicity and no evidence of induced autoimmunity.
- Broad coverage:
  - All dosing regimens yielded hSBA titers ≥1:8 in a high proportion of subjects against all 4 MnB test strains expressing epidemiologically relevant LP2086 variants that differ in sequence from variants included in the bivalent vaccine.
    - 86%–99% after 3 doses ($P<0.001$) and 69%–100% after 2 doses
- The data using heterologous test strains indicate the importance of the additional response provided by a 3-dose regimen.
- Global phase 3 clinical trials are underway with the bivalent rLP2086 vaccine.

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