Vaccine 34 (2016) 1465–1471

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

# A phase 3, randomized, active-controlled study to assess the safety and tolerability of meningococcal serogroup B vaccine bivalent rLP2086 in healthy adolescents and young adults☆

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ARTICLE INFO

*Article history:*
Received 5 August 2015
Received in revised form 14 January 2016
Accepted 19 January 2016
Available online 1 February 2016

*Keywords:*
Adolescents
Meningitis
Safety
Vaccine
Bivalent rLP2086

ABSTRACT

*Background: Neisseria meningitidis* serogroup B (MnB) is an important cause of invasive meningococcal disease (IMD). A MnB vaccine (bivalent rLP2086, Trumenba®) consisting of 2 factor H binding protein variants received accelerated approval in the United States for the prevention of IMD caused by MnB in individuals 10–25 years of age. This randomized, active-controlled, observer-blind study further assessed the safety and tolerability of bivalent rLP2086.

*Methods:* Eligible subjects ≥10 to <26 years were randomized (2:1) to receive bivalent rLP2086 at months 0, 2, and 6, or hepatitis A virus vaccine (HAV, Havrix®) at months 0 and 6, and saline at month 2. The primary endpoints were serious adverse events (SAEs) throughout the study and medically-attended adverse events (MAEs) within 30 days after vaccination. Additional safety assessments included SAEs at other study intervals and adverse events (AEs) during the vaccination phase.

*Results:* Of 5712 subjects randomized, 84.6% ($n$ = 3219) of bivalent rLP2086 recipients and 87.2% ($n$ = 1663) of HAV/saline recipients completed the study. Throughout the study, SAEs were reported for 1.6% and 2.5% of bivalent rLP2086 and HAV/saline recipients, respectively. SAEs related to either vaccine were rare. MAEs occurred in 7.0% and 6.1% of subjects after vaccination 1; 5.5% and 6.1% after vaccination 2; and 5.3% and 5.5% after vaccination 3 in the bivalent rLP2086 and HAV/saline groups, respectively. A greater proportion of subjects reported AEs during the vaccination phase after bivalent rLP2086 compared with HAV/saline recipients; however, when reactogenicity events were excluded, the proportion between groups was similar.

*Conclusion:* This safety study, the largest randomized, active-controlled trial evaluating a recombinant MnB vaccine, demonstrated that bivalent rLP2086 is safe and tolerable in healthy individuals ≥10 to <26 years of age.



*Abbreviations:* AE, adverse event; fHBP, factor H binding protein; HAV, hepatitis A virus vaccine; IMD, invasive meningococcal disease; MAE, medically-attended adverse event; MnB, *Neisseria meningitidis* serogroup B; NDCMC, newly-diagnosed chronic medical condition; SAE, serious adverse event.

☆ Clinical Trials Registration: NCT01352793.

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http://dx.doi.org/10.1016/j.vaccine.2016.01.044

## 1. Introduction

*Neisseria meningitidis* is a leading cause of invasive meningococcal disease (IMD) with peaks of incidence in children younger than 5 years, and in adolescents and young adults [1,2]. *N. meningitidis* caused by serogroup B (ie, capsular group B; MnB) is associated with approximately 75% of cases of meningococcal disease in Europe [2–4] and 20–50% of cases in the United States [5]. Mortality rates associated with IMD approach 20% [6–8], but many survivors experience sequelae such as hearing loss, seizures, and behavioral problems after meningococcal meningitis, and limb amputation, chronic pain and skin scarring after meningococcal septicemia [9].

Capsular polysaccharide conjugate vaccines are effective in preventing disease associated with *N. meningitidis* serogroups A, C, Y, and W-135 [10]. However, because of the homology of MnB capsular polysaccharides with polysialic acid structures present on human neural cells [11], MnB polysaccharide conjugate vaccines are not immunogenic [11]. The development of polysaccharide-based vaccines for this serogroup has not been possible. Alternative approaches have been necessary to identify meningococcal antigens for development of an effective vaccine protective against diverse MnB strains.

The *N. meningitidis* virulence factor LP2086 is a human factor H binding protein (fHBP) present on the surface of nearly all MnB strains [12,13]. Two genetically and immunologically distinct fHBP subfamilies (A and B) have been identified [12]. Bivalent rLP2086 (Trumenba®), is a prophylactic MnB vaccine consisting of equal amounts of recombinant subfamily A and B fHBP proteins. The vaccine elicits serum bactericidal antibodies that kill diverse MnB strains [14] expressing fHBPs from either subfamily, regardless of whether these have homologous or heterologous sequences compared with those in the vaccine [14–18]. Previous clinical studies demonstrated the safety, tolerability, and immunogenicity of bivalent rLP2086 in children, adolescents and young adults [14,16–19]. Based on these data, bivalent rLP2086 received accelerated approval from the US Food and Drug Administration in 2014 for the prevention of IMD caused by MnB in individuals 10–25 years of age [20,21]. In 2015, a second MnB vaccine, 4CMenB, which contains a non-lipidated form of fHBP from MnB subfamily B, was also licensed in the United States for the same population [21–24]. 4CMenB was previously licensed in the European Union and other regions for administration to individuals 2 months of age and older (through 17 years of age in Canada) [25–27].

This study assessed further the safety and tolerability of bivalent rLP2086 among adolescents and young adults aged ≥10 to <26 years when administered at 0, 2, and 6 months. This is the largest randomized, active-controlled study to date designed to investigate the safety of a recombinant MnB vaccine.

## 2. Methods

### 2.1. Study design

Subjects in this phase 3, randomized, active-controlled, observer-blind study were randomized 2:1 to receive bivalent rLP2086 at months 0, 2, and 6, or hepatitis A virus vaccine (HAV, Havrix®) at months 0 and 6, and saline at month 2. HAV was chosen because of the well-established safety profile of this vaccine [28]. Subjects were stratified into 10- to <19-year and 19- to <26-year cohorts to ensure adequate representation of adolescents and young adults. The study was conducted at 78 sites in Australia, Chile, Czech Republic, Denmark, Estonia, Finland, Germany, Lithuania, Poland, Spain, Sweden, and the United States between November 2012 and September 2014. The final protocol, any amendments, and informed consent document were reviewed and approved by the institutional review boards and/or independent ethics committees for each participating study site. The study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonisation Good Clinical Practice Guidelines, and local regulatory requirements. Written informed consent was obtained from all subjects (or their parents/legal guardians) before study enrollment and before performance of any study-related procedures.

### 2.2. Study objectives

The primary objective was to evaluate the safety of bivalent rLP2086 compared with HAV/saline, as assessed by serious adverse events (SAEs) throughout the study and medically-attended adverse events (MAEs) within 30 days after each vaccination. Secondary objectives were to evaluate the safety profile of bivalent rLP2086 vaccine compared with HAV/saline, as measured by adverse events (AEs), SAEs, newly-diagnosed chronic medical conditions (NDCMCs), MAEs, immediate AEs and missed days of school/work at various study intervals. Immunogenicity data were not collected.

### 2.3. Study participants

Primary inclusion criteria were healthy males or females ≥10 to <26 years of age at enrollment available for the entire study period. Sexually active subjects of childbearing potential had to agree to use a highly effective method of contraception throughout the study. Key exclusion criteria were receipt of a previous MnB or HAV vaccine, contraindication for HAV vaccination, scheduled to receive ≥1 dose of human papillomavirus vaccine between visit 1 and 28 days after vaccination 2, experienced a previous anaphylactic reaction to any vaccine or vaccine-related component, a history of microbiologically-proven disease caused by *N. meningitidis* or *N. gonorrhea*, or current pregnancy or breastfeeding.

### 2.4. Vaccines administered

Bivalent rLP2086 (120 μg) was formulated and administered as previously described [17]. HAV contains 720 ELISA units (EL.U.) or 1440 EL.U. of viral antigen per 0.5-mL or 1.0-mL dose, respectively. Age-specific doses of HAV were administered according to country-specific guidelines. Placebo consisted of normal sterile saline solution for injection (0.9% sodium chloride) supplied as a 0.5-mL dose. Vaccines or placebo were administered into the upper deltoid muscle of the arm with a 25-gauge, 1-inch needle.

### 2.5. Safety and tolerability assessments

Safety information was collected during monthly visits/contacts between months 0 and 7 (the vaccination phase) and approximately 6 months after the last vaccination (the follow-up phase). The primary endpoints were the percentage of subjects with ≥1 SAE during the study period (the vaccination through follow-up phases), and the percentage of subjects with ≥1 MAE occurring within 30 days after each vaccination. Secondary endpoints were the percentage of subjects with ≥1 SAE, MAE, NDCMC, AE, and immediate AE occurring during specific analysis intervals; and the percentage of subjects who missed days of school or work because of AEs. NDCMCs (as reported by the investigator) were defined as a disease or medical condition, not previously identified, that was expected to be persistent or otherwise long-lasting in its effects. MAEs were non-serious AEs requiring evaluation at a healthcare facility. Immediate AEs were those that occurred within the first 30 min after study vaccination. Electronic diaries were not used as