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Persistence and 4-year boosting of the bactericidal response elicited by two- and three-dose schedules of MenB-FHbp: A phase 3 extension study in adolescents

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ABSTRACT

Background: The period of heightened risk of invasive meningococcal disease in adolescence extends for >10 years. This study aimed to evaluate persistence of the immune response to the serogroup B meningococcal (MenB) vaccine MenB-FHbp (Trumenba®, Bivalent rLP2086) under two- and three-dose primary vaccination schedules, both of which are approved in the United States and the European Union, and to assess safety and immunogenicity of a booster dose.

Methods: This was an open-label extension study of a phase 2 randomized MenB-FHbp study (primary study). This interim analysis includes data through 1 month after booster vaccination. In the primary study, adolescents 11–18 years of age were randomized using an interactive voice or web-based response system to receive 120 μg MenB-FHbp under 0-, 1-, 6-month; 0-, 2-, 6-month; 0-, 6-month; 0-, 2-month; or 0-, 4-month schedules (termed study groups for the current analysis). For the primary study, participants were blinded to their vaccine study group allocation, but investigators and the study sponsor were unblinded. Immune responses in subjects from the primary study were evaluated through 48 months after primary vaccination (persistence stage; 17 sites in Czech Republic, Denmark, Germany, and Sweden). Safety and immunogenicity of a booster dose given at 48 months after primary vaccination (booster stage; 14 sites in Czech Republic, Denmark, and Sweden) were also assessed. Immune responses were evaluated in serum bactericidal assays with human complement (hSBAs) using four MenB test strains representative of disease-causing MenB strains in the United States and Europe and expressing factor H binding proteins (FHbps) heterologous to the vaccine antigens. The primary immunogenicity endpoints were the proportions of subjects with hSBA titers greater than or equal to the assays' lower limit of quantitation (LLOQ; 1:8 or 1:16 depending on strain) at 12, 18, 24, 36, and 48 months after primary vaccination (persistence stage) and 1 and 48 months after the primary vaccination series and 1 month after receipt of the booster dose (booster stage). Safety evaluations during the booster stage included local reactions and systemic events by severity, antipyretic use, adverse events (AEs), immediate AEs, serious AEs (SAEs), medically attended AEs (MAEs), newly diagnosed chronic medical conditions (NDCMCs), and missed days of school and work because of AEs. The modified intent-to-treat (mITT) population was used for immunogenicity evaluations in the persistence stage. The booster stage immunogenicity evaluations used the evaluable immunogenicity population; analyses were also performed in the mITT population. For the persistence stage, safety evaluations included subjects with at least one blood draw, whereas for the booster stage, they included subjects who received the booster dose and had available safety data. This trial is registered at ClinicalTrials.gov number NCT01543087.

Findings: A total of 465 subjects were enrolled in the persistence stage, and 271 subjects were enrolled in the booster stage. Sera for the extension phase of this interim analysis were collected from September 7,

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2012 to December 7, 2015. One month after primary vaccination, 73.8–100.0% of subjects depending on study group responded with hSBA titers ≥LLOQ. Response rates declined during the 12 months after last primary vaccination and then remained stable through 48 months, with 18.0–61.3% of subjects depending on study group having hSBA titers ≥LLOQ at this time point. One month after receipt of the booster dose, 91.9–100.0% of subjects depending on study group had hSBA titers ≥LLOQ against the four primary strains individually and 91.8–98.2% had hSBA titers ≥LLOQ against all four strains combined (composite response). Geometric mean titers were higher after booster vaccination than at 1 month after primary vaccination. Immune responses were generally similar across study groups, regardless of whether a two- or three-dose primary series was received. None of the AEs (2.2–6.9% of subjects depending on study group) or NDCMCs (1.8–5.0%) that were reported during the persistence stage were considered related to the investigational product. Local reactions and systemic events were reported by 84.4–93.8% and 68.8–76.6% of subjects depending on study group, respectively, in the booster stage; these were generally similar across study groups, transient, and less frequent than after any primary vaccination. Additionally, there was no general progressive worsening in severity of reactogenicity events (ie, potentiation; ≤3 subjects per group), and reactogenicity events did not lead to any study withdrawals. No NDCMCs or immediate AEs were reported during the booster stage. AEs were reported by 3.7–12.5% of subjects depending on study group during the booster stage. The two possibly related AEs included a mild worsening of psoriasis and a severe influenza-like illness that resolved in 10 days.

Interpretation: Immune responses declined after the primary vaccination series; however, a substantially greater number of subjects retained protective responses at 48 months after primary vaccination compared with subjects having protective responses before vaccination. Persistence trends were similar across all 5 study groups regardless of whether a two- or three-dose primary schedule was received. Furthermore, a booster dose given 48 months after primary vaccination was safe, well-tolerated, and elicited robust immune responses indicative of immunologic memory; these responses were similar between two- and three-dose primary schedule study groups. Use of a booster dose may help further extend protection against MenB disease in adolescents.

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1. Research in context

1.1. Evidence before this study

PubMed was searched for articles published between January 1, 2010, and November 30, 2017, using the search term "(persistence OR booster) AND vaccine AND (meningococcal OR (Neisseria meningitidis) OR (N meningitidis)) AND (adolescent OR (young adult))." The search returned 101 articles; of these, 92 were excluded because the title and/or abstract indicated that the article did not relate results from a clinical study (n = 48), did not concern subjects initially vaccinated as adolescents and/or young adults (n = 2), were not performed in healthy participants (n = 1), did not assess immunologic persistence and/or receipt of a booster dose (n = 14), used serum bactericidal antibody assays with rabbit complement (rSBA) rather than with human complement (hSBA) or did not assess SBA at all (n = 19), or had follow-up times ≤2 years in the case of persistence studies or assessed administration of a booster dose ≤2 years after primary vaccination (n = 8). Upon review of full article texts, three additional articles were excluded because rSBA rather than hSBA was used. Two additional articles concerned the same study; only the most recent article was included.

The 5 articles retained for further analysis demonstrated that immune responses to various meningococcal serogroups A, C, W, and Y (MenACWY) capsular polysaccharide conjugate vaccines in adolescents and/or young adults waned over periods of ≥3 years; however, booster doses of these vaccines elicited robust immune responses. Data for meningococcal serogroup B (MenB) vaccines in this age group were limited. The one study addressing MenB vaccine persistence demonstrated that immune responses to MenB-FHbp (Trumenba®, Bivalent rLP2086) similarly waned over time but that a majority of subjects had protective titers against three of four MenB test strains at 4 years postvaccination. There were no studies identified that assessed booster vaccination with a MenB vaccine in adolescents and/or young adults.

1.2. Added value of this study

MenB-FHbp is currently approved in various countries under two- (0 and 6 months) and three-dose (0, 1–2, and 6 months) primary schedules, which were demonstrated in an earlier study (termed the "primary study" throughout this report) to elicit similar immune responses. However, there is no published evidence comparing immunologic persistence across these schedules in adolescents and/or young adults, who require continued protection from meningococcal disease because of their extended period of increased risk. Furthermore, there are no published studies assessing immune responses to a MenB booster dose, which may help extend protection, as in the case of MenACWY vaccines. The current study thus evaluated immunologic persistence in subjects from the primary study who received two- or three-dose primary series of MenB-FHbp for 4 years after primary vaccination as well as the safety and immunogenicity of a booster dose given at the 4-year time point.

1.3. Implications of all available evidence

Persistence of immune responses showed similar patterns regardless of the primary MenB-FHbp vaccination schedule. The booster dose given at 4 years after primary vaccination elicited robust immune responses indicative of immunologic memory that were similar between groups receiving two- (0 and 6 months) and three-dose (0, 1–2, and 6 months) primary schedules and was associated with a lower frequency of local and systemic reactions in comparison with any vaccination during the primary series. These data thus provide important support for the continued use of approved two- and three-dose primary MenB-FHbp dosing schedules. As persistence and booster immune responses to both two- and three-dose primary schedules were similar, the choice of schedule should be based on an individual's susceptibility to disease, with a three-dose schedule preferred for those at increased risk (eg, due to an outbreak or a specific medical condition) and

a 0-, 6-month schedule for individuals not considered to be at increased risk. Persistence data through 26 months after the booster dose are forthcoming and will further inform any potential differences in two- and three-dose primary vaccination schedules.

2. Introduction

Invasive meningococcal disease (IMD) is a devastating illness caused by the pathogen *Neisseria meningitidis* [1]. Although IMD is rare [1], the case fatality rate is about 10% [2], and a high proportion of survivors experience serious sequelae, such as neurologic impairments and hearing loss [2]. Most IMD is caused by *N meningitidis* belonging to serogroups A, B, C, W, X, and Y [3]. Serogroup B IMD (MenB) represented approximately one-third of all IMD cases in the United States during 2002–2011 [1] and two-thirds of all cases in Europe in 2014 [4]. Most European countries as well as Australia, New Zealand, South Africa, and some South American countries have MenB incidence rates similar to or higher than the United States, and several other countries (eg, Japan, Morocco, Israel) have reported MenB predominance in their respective countries [5].

Polysaccharide conjugate vaccines targeting serogroups A, C, W, and Y are highly immunogenic [6,7]. However, polysaccharide-based MenB vaccines have demonstrated poor immunogenicity [8,9], likely because the serogroup B polysaccharide is identical to a polysaccharide native to the human brain [9]. Successful MenB vaccines previously used were instead based on outer membrane vesicles, but resulting protection was generally strain-specific and short-lasting [10]. Recent advances led to the development of MenB vaccines designed to provide broad protection against diverse invasive MenB strains.

MenB-FHbp (Trumenba®, Bivalent rLP2086; Pfizer Inc, Philadelphia, PA), one such vaccine, is composed of two factor H binding proteins (FHbps), one from each FHbp subfamily (A and B) [11]; MenB-FHbp became the first MenB vaccine licensed in the United States in October 2014 [11] and received EU licensure in May 2017 [12]; approval has also recently been received in other countries. MenB-FHbp is licensed and recommended under a three-dose schedule given at 0, 1–2, and 6 months or a two-dose schedule given at 0 and 6 months, with disease susceptibility influencing choice of dosing schedule [12,13].

Adolescents and young adults have disproportionately high rates of IMD [1] and are also the primary carriers of meningococci [14]. Thus, this age group represents an important target for meningococcal vaccination. Importantly, heightened risk extends for more than a decade [1], so vaccination should ideally provide protection during this entire period.

Previously, quadrivalent meningococcal capsular polysaccharide conjugate vaccine (MenACWY vaccine) persistence studies have shown that immune responses after primary vaccination with a single dose decline over several years [15–17], with recent data suggesting that vaccine effectiveness correspondingly deteriorates [18]; a single dose is therefore insufficient to provide protection throughout adolescence and young adulthood. However, additional MenACWY vaccine doses given 3–6 years after primary vaccination have been shown to confer robust immune responses [15–17]. Such data collectively led the US Advisory Committee on Immunization Practices to routinely recommend a booster dose of MenACWY vaccine at age 16 years after primary immunization at age 11–12 years [19]. There are no published studies assessing safety and immunogenicity of a MenB-FHbp booster dose in adolescents or young adults.

Based on experience with MenACWY vaccines, it is important to evaluate persistence of the immune response to MenB vaccines, as well as safety and immunogenicity of a potential booster dose. This study thus sought to evaluate persistence of the immune response induced by a two- or three-dose primary MenB-FHbp series over 4 years, as well as safety and immunogenicity of a booster dose administered 4 years after the primary series. The current study includes data through 1 month after booster vaccination; data from later time points will be published when available.

3. Methods

3.1. Study design and participants

This phase 3 study was an open-label extension of three previously conducted phase 2 studies (primary studies; ClinicalTrials.gov NCT01323270, NCT01299480, and NCT01461980). This interim analysis was planned to occur after all enrolled subjects from one of these primary studies (ClinicalTrials.gov NCT01299480) completed the visit occurring 1 month after the booster vaccination and presents results from sera collected from September 2012 through December 2015, along with some data from the primary study for reference. Subjects from the other two studies (ClinicalTrials.gov NCT01323270 and NCT01461980) had not yet completed the corresponding study visits. The primary study from which subjects were included in this interim analysis was a randomized, placebo-controlled, single-blind, multicenter study in adolescents 11–18 years of age from the Czech Republic, Denmark, Finland, Germany, Poland, Spain, and Sweden who were randomized to receive MenB-FHbp under one of the following schedules: 0, 1, 6 months (Group 1); 0, 2, 6 months (Group 2); 0, 6 months (Group 3); 0, 2 months (Group 4); or 0, 4 months (Group 5) [20]. These five primary study dosing schedule groups are hereafter referred to as study groups.

The extension study consisted of two stages, the persistence and booster stages. In the persistence stage, subjects from 17 sites in the Czech Republic, Denmark, Germany, and Sweden who completed the primary study were evaluated to assess immune response persistence at 12, 18, 24, 36, and 48 months after the last primary dose. Inclusion criteria were completion of the primary study, including the blood draw after the last vaccination and the 6-month follow-up safety telephone call, documentation of informed consent, and compliance with primary study procedures.

The booster stage included a MenB-FHbp booster dose administered approximately 48 months after receipt of the primary series through subject evaluation at 1 month after booster vaccination. All sites from the primary study that participated in the persistence stage and agreed to participate in the booster stage were selected, provided necessary approvals were obtained; the one exception was one site not selected because of low expected enrollment yield (1 potentially eligible subject). There was no consideration of subjects' prior serum bactericidal assays with human complement (hSBA) responses in booster site selection. Ultimately, 14 sites in the Czech Republic, Denmark, and Sweden participated in the booster stage. Within each participating site, subjects eligible for the booster stage were those who completed the persistence stage, continued to meet the persistence stage eligibility criteria, were available for the duration of the booster stage, were judged to be healthy and not pregnant, agreed to use an effective form of contraception, and had documented informed consent.

Several important amendments were made to the study design after trial commencement. In December 2013, changes included modification of study objectives and endpoints, increasing the number of subjects to be enrolled, and updating safety data collection and reporting. Inclusion criteria were also updated to allow enrollment of subjects whose vaccine assignment was blinded at the time of study entry, and exclusion criteria were modified to prohibit enrollment of subjects who did not comply with primary

study eligibility criteria. In January 2015, an additional amendment added the booster stage to the protocol and accompanying safety and immunogenicity assessments.

The final protocol, any amendments, and informed consent forms were reviewed by institutional review board(s) and/or independent ethics committee(s) for each site. Consent was obtained before enrollment in the persistence stage and again before enrollment in the booster stage; consent was renewed for any subjects reaching the age of majority, according to local law, during the study. The study followed ethical principles from the Declaration of Helsinki and guidelines from the International Council on Harmonisation Good Clinical Practice.

3.2. Randomization and masking

For the primary study, subjects were randomized by an interactive voice response system (IVRS) or interactive web-based response system (IWRS) or equivalent. The dispenser accessed the system through a user identification and password and entered study and subject information. The dispenser was then provided with a subject randomization number, vaccine assignment and package number. The subject randomization number was recorded and confirmation of randomization was sent to the subject. Subjects, but not investigators or the study sponsor, were blinded to their allocated vaccine groups.

The extension study was open-label. An IVRS, IWRS, or equivalent was used similar to the primary study to assign study numbers and track study visits.

3.3. Procedures

Subjects participating in the booster stage received 0.5 mL MenB-FHbp injected into the deltoid muscle at approximately 48 months after receipt of the last primary series dose.

Included in this interim analysis are immune responses of subjects at 12, 18, 24, 36, and 48 months after completion of the primary series and at 1 month after receipt of the booster dose. Responses were evaluated using validated hSBAs using four MenB test strains: PMB80 (containing FHbp variant A22), PMB2001 (A56), PMB2948 (B24), and PMB2707 (B44). These test strains all express FHbps heterologous in sequence to those contained in MenB-FHbp and represent four of the six major FHbp phylogenetic subgroups, which collectively are expressed by approximately 91% of disease-causing MenB strains in the United States and Europe [21]. Additionally, the four test strains are representative of >80% of disease-causing strains in terms of clonal complexes. These test strains were used in hSBAs to evaluate the immune response to MenB-FHbp in multiple other clinical studies [20,22–24]. For comparison, sera obtained during the primary study at 1 month after the last primary series vaccination were reevaluated concurrently with sera obtained from visits during the current study.

3.4. Outcomes

The persistence stage primary immunogenicity endpoint was the proportion of subjects with hSBA titers greater than or equal to the lower limit of quantitation (LLOQ; 1:16 for the test strain expressing FHbp variant A22, 1:8 for the other test strains) against the four MenB test strains at 12, 18, 24, 36, and 48 months after receipt of the last primary series dose. The booster stage primary immunogenicity endpoint was the proportion of subjects with hSBA titers $\geq$LLOQ against the four MenB test strains at 1 month after the primary series, before booster vaccination (month 48), and at 1 month after the booster dose.

For both stages, exploratory immunogenicity endpoints included the proportions of subjects with hSBA titers $\geq$1:4 (the accepted correlate of protection for IMD [25–27]), $\geq$1:8, $\geq$1:16, $\geq$1:32, $\geq$1:64, and $\geq$1:128 as well as hSBA geometric mean titers (GMTs) against the four MenB test strains measured at each blood draw visit. An additional exploratory endpoint for the booster stage included evaluating subjects with a composite response (hSBA titers $\geq$LLOQ against all four strains combined) at 1 month after the last primary series dose, before booster vaccination (month 48), and at 1 month after the booster dose.

During the persistence stage, nonserious adverse events (AEs) and research-related injuries (RRIs) were reportable in the first 48 h after each blood draw. Newly diagnosed chronic medical conditions (NDCMCs) were also recorded throughout the persistence stage.

During the booster stage, local reactions (redness, swelling, and injection site pain), systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, muscle pain other than at the injection site, and joint pain), and antipyretic medication use were collected using an electronic diary for 7 days after MenB-FHbp booster dose administration; these were considered solicited AEs. AEs (serious and nonserious), medically attended adverse event (MAE), and NDCMCs were also collected. Immediate AEs (those occurring within 30 min of MenB-FHbp administration) were also reported. Nonserious AEs were reported from the time of informed consent through the visit occurring 1 month after booster vaccination and within 48 h of the blood draw occurring at that visit. Serious AEs (SAEs), MAEs, and NDCMCs were reported throughout the booster stage.

Primary safety endpoints during the booster stage included (1) percentages of subjects reporting local reactions and systemic events by severity, and antipyretic medication use after booster vaccination; (2) percentages of subjects with at least one AE, SAE, NDCMC, or MAE occurring during the booster stage; (3) percentage of subjects reporting at least one immediate AE after booster administration; and (4) number of missed days from school or work because of AEs during the booster stage.

3.5. Statistical analysis

As an extension study, sample size determination was not dictated by statistical analyses. The overall study (including participants from three different primary studies) aimed to enroll 800 subjects to allow sufficient numbers for subgroup analysis; no sample size from the primary study included in the current analysis was prespecified.

The persistence stage immunogenicity analysis used the modified intent-to-treat (mITT) population, which included all subjects who had at least one valid and determinate assay result in this stage. The booster stage immunogenicity analysis used the evaluable immunogenicity population, which included subjects who (1) were eligible for the booster stage, (2) received the investigational product as intended, (3) had a prebooster vaccination blood draw and a blood draw within 28–42 days after booster vaccination, (4) had a valid and determinate assay result for the proposed analysis, (5) did not receive any prohibited vaccines or treatment, and (6) had no other major protocol violations. Immunogenicity analyses for the booster stage were also performed in the booster mITT population, which for this stage included all subjects who received the booster dose and had at least one valid and determinate assay result in this stage.

In the persistence stage, the safety population included any subject with at least one blood draw, whereas for the booster stage, it included any subject who received the booster vaccination and for whom safety data were available.

Demographic and safety analyses are descriptive. For hSBA data analysis, titers were logarithmically transformed for calculation of GMTs at each time point. Corresponding two-sided 95% CIs were

calculated for the mean of the logarithmically transformed data based on Student *t* distribution and then back-transformed to the original scale. For titers less than the LLOQ, GMT calculations used a value of half the LLOQ. For binary endpoints (ie, those measuring proportions of subjects), exact two-sided 95% CIs were calculated using the Clopper-Pearson method.

Statistical analyses were performed using SAS (version 9.3; SAS Institute Inc., Cary, NC). The study is registered as ClinicalTrials.gov number NCT01543087.

3.6. Role of the funding source

The sponsor of the study was involved in study design, data collection, data analysis, data interpretation, writing of the study report, and the decision to submit the paper for publication. The corresponding author had full access to the study data and had final responsibility for the decision to submit the paper for publication.

4. Results

Enrollment for the persistence stage extended from September 7, 2012, to October 29, 2012. Of the 1550 patients who completed the primary study (Group 1 = 385; Group 2 = 395; Group 3 = 386; Group 4 = 261; Group 5 = 123), 465 (30%) enrolled in the persistence stage (Group 1 = 103 [27%]; Group 2 = 114 [29%]; Group 3 = 116 [30%]; Group 4 = 86 [33%]; Group 5 = 46 [37%]). The persistence stage was completed by 88.6–100.0% of these subjects, depending on study group (Fig. 1). Common reasons for subject withdrawals during this stage were lost to follow-up and no longer willing to participate in the study. Subjects were enrolled in the booster stage (n = 32–64 depending on study group) from May 27, 2015, to November 4, 2015; 96.4–100.0% of these subjects received the booster vaccination and completed the 1 month postbooster visit.

Three subjects who were enrolled in the booster stage were withdrawn before booster vaccination, with reasons including the following: no longer willing to participate, ineligible, and scheduling difficulties (Fig. 1). No subjects withdrew because of AEs. Six subjects were excluded from the booster stage-evaluable immunogenicity population for reasons including ineligibility or becoming ineligible during the booster stage, not receiving the booster vaccination as intended, not having a scheduled prevaccination or postvaccination blood draw, or not having a valid and determinate assay result from either of these blood draws. Demographic characteristics were similar across study groups for both stages (Table 1).

In the primary study, longer intervals between the first two doses generally resulted in more robust immune responses, with the subjects in the 0-, 6-month group demonstrating responses similar to those in the three-dose groups [20]. In the three-dose groups, two doses given in rapid succession (ie, 1 or 2 months between the first 2 doses) elicited a robust immune response that was further augmented by a third dose given at 6 months.

During the persistence stage of the current study, percentages of subjects with hSBA titers ≥LLOQ declined from levels observed at 1 month after the last primary series dose and plateaued by 12 months after the last primary series dose (Fig. 2, Table S1). At 1 month after the last primary dose, percentages ranged from 73.8–100.0% across strains and study groups. For the MenB test strain expressing FHbp variant A22, percentages of subjects with hSBA titers ≥LLOQ across groups declined to a range of 36.3–45.0% at 12 months after the last primary dose and to a range of 39.6–45.7% at 48 months after the last primary dose. For the test strain expressing FHbp variant A56, percentages of subjects with hSBA titers ≥LLOQ across groups ranged from 60.4–76.1% at 12 months after the last primary dose and from 47.1–61.3% at 48 months after the last primary dose. For the test strain expressing FHbp variant B24, percentages of subjects with hSBA titers ≥LLOQ across groups ranged from 36.9–49.1% at 12 months after the last primary dose and from 30.5–45.1% at 48 months after the last primary dose. For the test strain expressing FHbp variant B44, percentages of subjects with hSBA titers ≥LLOQ across groups ranged from 16.5–24.0% at 12 months after the last primary dose and from 18.0–24.4% at 48 months after the last primary dose. Immune responses from 12 months after the last primary series dose through 48 months were generally similar across study groups regardless of whether two or three doses were administered for the primary series. hSBA GMTs demonstrated a similar

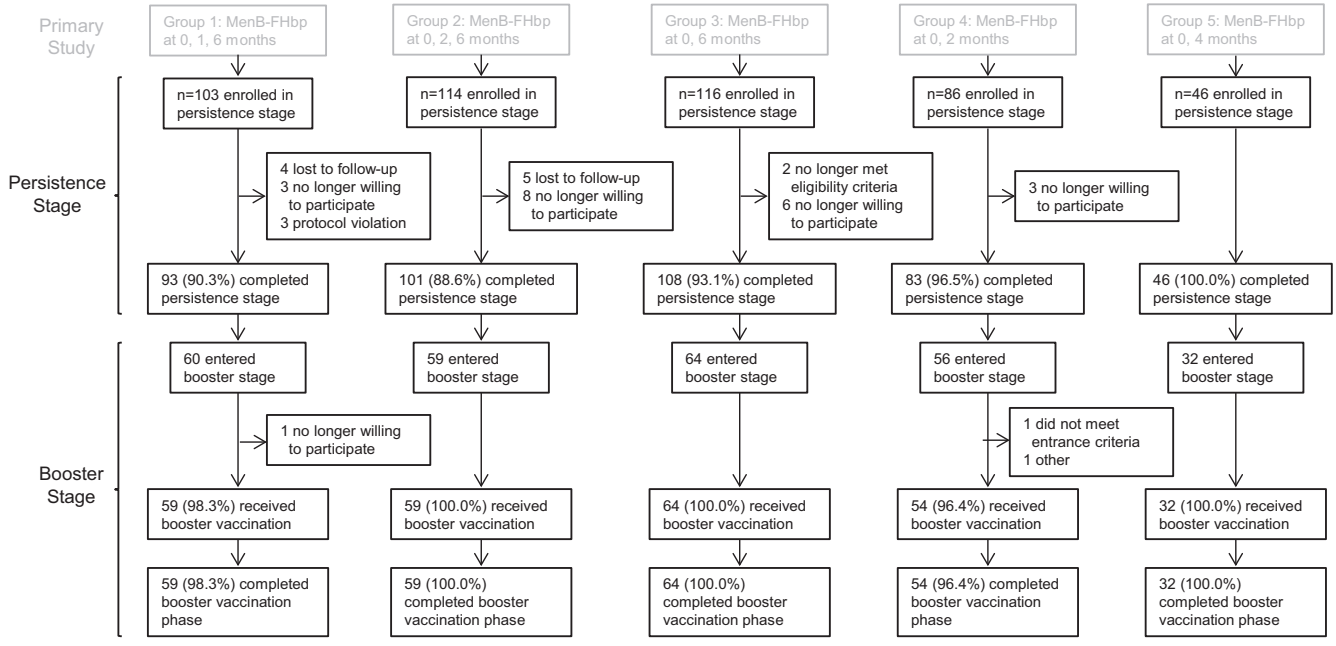

Fig. 1. CONSORT diagram with subject disposition.

Table 1
Demographic characteristics of study participants.

	Persistence Stage Primary Study Group (as Administered)					Booster Stage Primary Study Group (as Administered)				
	0-, 1-, 6-Month Schedule (N = 101) n (%)	0-, 2-, 6-Month Schedule (N = 114) n (%)	0-, 6-Month Schedule (N = 116) n (%)	0-, 2-Month Schedule (N = 86) n (%)	0-, 4-Month Schedule (N = 46) n (%)	0-, 1-, 6-Month Schedule (N = 59) n (%)	0-, 2-, 6-Month Schedule (N = 59) n (%)	0-, 6-Month Schedule (N = 64) n (%)	0-, 2-Month Schedule (N = 54) n (%)	0-, 4-Month Schedule (N = 32) n (%)
Sex										
Male	48 (47.5)	47 (41.2)	49 (42.2)	48 (55.8)	20 (43.5)	29 (49.2)	20 (33.9)	28 (43.8)	29 (53.7)	14 (43.8)
Female	53 (52.5)	67 (58.8)	67 (57.8)	38 (44.2)	26 (56.5)	30 (50.8)	39 (66.1)	36 (56.3)	25 (46.3)	18 (56.3)
Race										
White	101 (100.0)	114 (100.0)	115 (99.1)	85 (98.8)	46 (100.0)	59 (100.0)	59 (100.0)	64 (100.0)	53 (98.1)	32 (100.0)
Black	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)					
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)
Ethnicity										
Non-Hispanic/non-Latino	101 (100.0)	114 (100.0)	115 (99.1)	84 (97.7)	46 (100.0)	59 (100.0)	59 (100.0)	63 (98.4)	53 (98.1)	32 (100.0)
Hispanic/Latino	0 (0.0)	0 (0.0)	1 (0.9)	2 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.9)	0 (0.0)
Age at first vaccination in primary study, years										
10–14	53 (52.5)	50 (43.9)	62 (53.4)	40 (46.5)	24 (52.2)	30 (50.8)	28 (47.5)	35 (54.7)	22 (40.7)	18 (56.3)
15–18	48 (47.5)	64 (56.1)	54 (46.6)	46 (53.5)	22 (47.8)	29 (49.2)	31 (52.5)	29 (45.3)	32 (59.3)	14 (43.8)
Mean (SD)	14.3 (2.2)	14.6 (2.3)	14.2 (2.1)	14.6 (2.4)	14.4 (2.2)	14.5 (2.4)	14.4 (2.3)	14.3 (2.1)	14.8 (2.5)	14.1 (2.2)
Median	14.0	15.0	14.0	15.0	14.0	14.0	15.0	14.0	15.0	14.0
Min, max	11, 18	11, 18	11, 18	11, 18	11, 18	11, 18	11, 18	11, 18	11, 18	11, 18
Age at enrollment in stage, years										
10–14	34 (33.7)	34 (29.8)	38 (32.8)	26 (30.2)	11 (23.9)					
15–18	51 (50.5)	59 (51.8)	61 (52.6)	44 (51.2)	27 (58.7)	27 (45.8)	27 (45.8)	29 (45.3)	20 (37.0)	17 (53.1)
>18	16 (15.8)	21 (18.4)	17 (14.7)	16 (18.6)	8 (17.4)	32 (54.2)	32 (54.2)	35 (54.7)	34 (63.0)	15 (46.9)
Mean (SD)	15.9 (2.2)	16.2 (2.2)	15.8 (2.1)	16.1 (2.4)	15.9 (2.1)	18.9 (2.3)	18.9 (2.3)	18.8 (2.1)	19.0 (2.6)	18.7 (2.2)
Median	16.0	17.0	16.0	16.5	16.0	19.0	19.0	19.0	19.5	18.0
Min, max	12, 20	12, 20	12, 20	12, 20	12, 20	15, 23	15, 23	15, 22	15, 23	15, 23

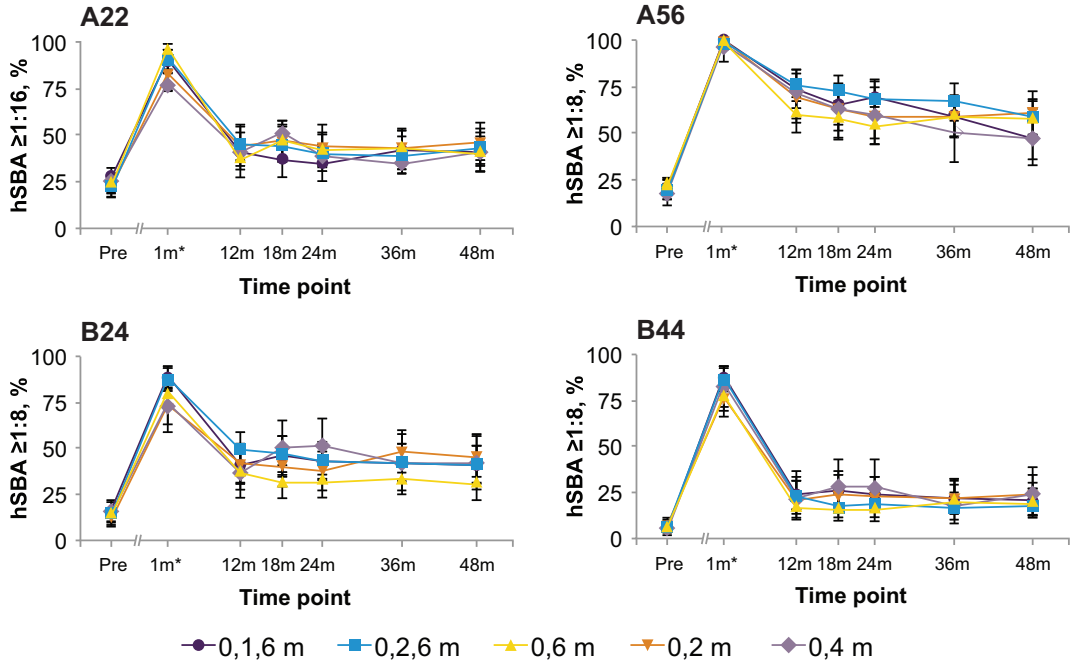

Fig. 2. Percentages of subjects achieving hSBA titers ≥LLOQ against each of the 4 primary strains by time point during the persistence stage. Error bars represent 95% CIs. *Interval between prevaccination and 1 month post primary vaccination varies by group. hSBA = serum bactericidal assay with human complement; LLOQ = lower limit of quantitation.

pattern to percentages of subjects achieving hSBA titers ≥LLOQ (Fig. S1). One month after the last primary series dose, the percentages of subjects in the three-dose study groups that achieved hSBA titers ≥1:4 against the MenB test strains were as follows across groups: A22, 91.0–92.0%; A56, 99.1–100.0%; B24, 89.5–90.0%; B44, 89.2–91.9%, whereas these ranges across the two-dose study groups were A22, 80.4–96.5%; A56, 97.8–100.0%; B24, 73.8–81.4%; B44, 79.0–89.1%. By 48 months after the last dose, these

percentages in the three-dose study groups were as follows across groups: A22, 45.0–45.6%; A56, 48.2–60.6%; B24, 41.8–43.3%; B44, 24.0–28.3%. In the two-dose study groups, percentages were A22, 39.6–49.4%; A56, 50.0–61.6%; B24, 31.4–45.1%; B44, 24.5–34.8% across groups.

In the booster stage, 91.9–100.0% of subjects achieved hSBA ≥LLOQ at 1 month after receipt of the MenB-FHbp booster dose (Fig. 3A, Table S2); these percentages were generally comparable to or higher than those at 1 month after receipt of the last primary dose. Results were generally similar across study groups regardless of whether a two- or three-dose primary series schedule was received. As in the persistence stage, hSBA GMTs in the booster stage (Fig. 3B) followed a similar pattern to percentages of subjects achieving hSBA titers ≥LLOQ (Fig. 3A). Importantly, GMTs 1 month after the booster dose were substantially higher than at 1 month after the last primary series vaccination regardless of whether a two- or three-dose primary schedule was received. At 1 month after the booster dose, 96.6–100.0% of subjects in the three-dose study groups and 91.9–100.0% in the two-dose study groups achieved hSBA titers ≥1:4.

At 1 month after receipt of the last primary series dose, 58.0–87.3% of subjects depending on study group in the booster stage-evaluable immunogenicity population achieved a composite response (Table S3); this decreased to 15.7–23.4% at 48 months, but increased to 91.8–98.2% at 1 month after booster vaccination. Immunogenicity results using the booster mITT population for

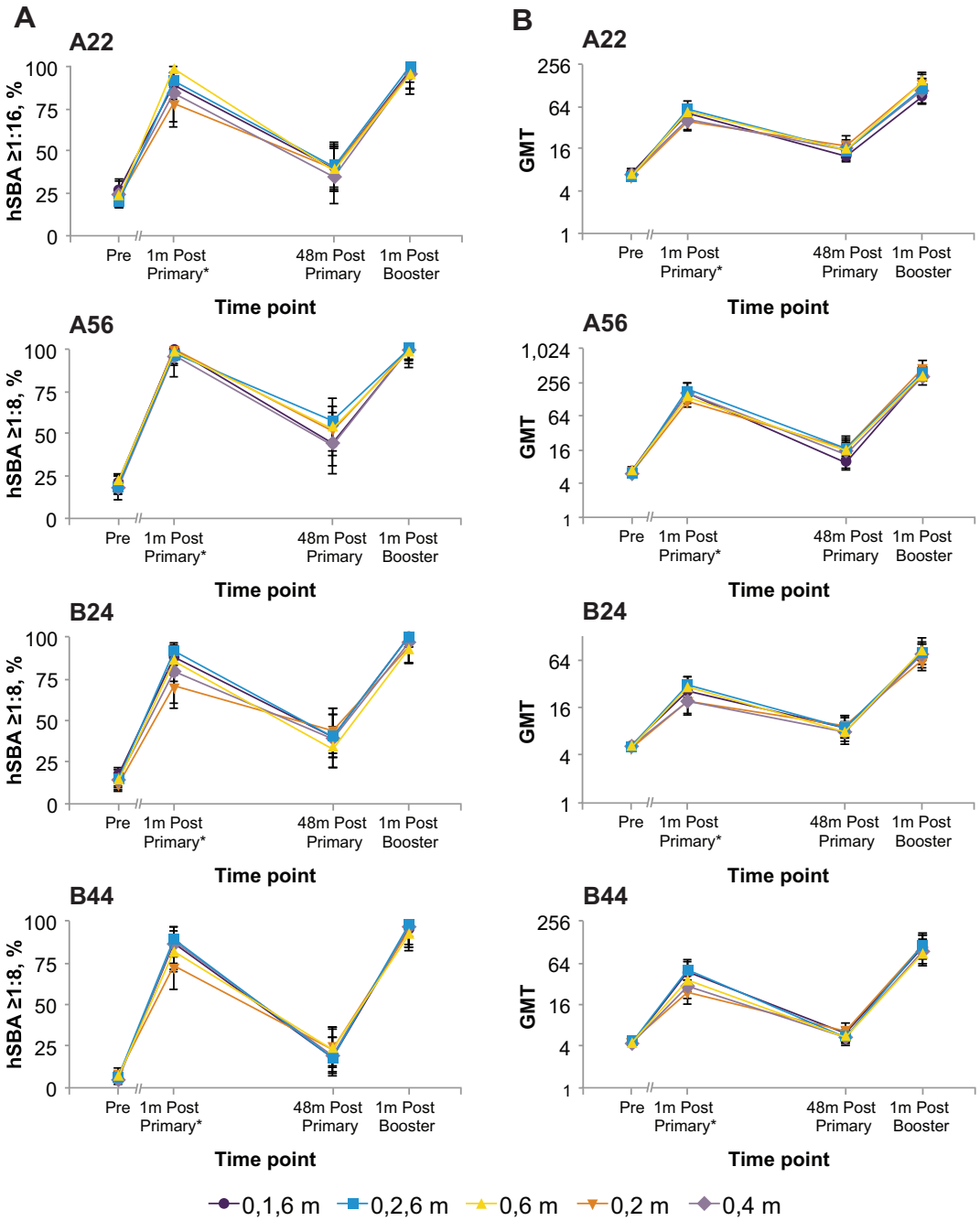

Fig. 3. (A) Percentages of subjects achieving hSBA titers ≥LLOQ and (B) GMTs against each of the 4 primary strains by time point during the booster stage. Error bars represent 95% CIs. *Interval between prevaccination and 1 month post primary vaccination varies by group. GMT = geometric mean titer; hSBA = serum bactericidal assay with human complement.

the booster stage were similar to those calculated for the evaluable immunogenicity population.

Throughout the persistence stage, 2.2–6.9% of subjects across study groups reported at least one AE; all AEs were mild or moderate in severity and none were deemed related to the investigational product. No RRIs were reported throughout the persistence stage. NDCMCs were reported by 1.8–5.0% of subjects depending on study group during the persistence stage; all were deemed unrelated to MenB-FHbp.

For the booster stage, the percentages of subjects in the 0-, 2-, 6- and 0-, 6-month study groups reporting local reactions within 7 days after any primary vaccination or the booster vaccination are shown in Fig. 4A; Fig. S2A displays local reactions for all study groups. Overall, 84.4–93.8% of subjects reported local reactions across study groups. Pain at the injection site was the most commonly reported local reaction. Percentages of subjects reporting local reactions after the booster dose were generally lower than those reporting local reactions after any vaccination in the primary study. The median duration of local reactions after booster vaccination was 3 days for pain at the injection site, 2–3 days for redness, and 1–3 days for swelling. Few subjects (≤3 in each study group) reported a "severity increase with potentiation," defined as an increase in severity of the same reaction after each MenB-FHbp dose and either (1) increased severity of the same type after the booster dose compared with the last primary dose or (2) a severe reaction after the booster dose. No subjects withdrew due to local reactions.

Percentages of subjects reporting systemic events in the booster stage were similar across study groups, with 68.8–76.6% of all subjects depending on study group reporting at least one systemic event. All fevers reported in the booster stage (≤5.1% of subjects across study groups; Fig. 4B and S2B) were <39 °C. The most commonly reported systemic events (Fig. 4C and S2C) were fatigue and headache, with percentages of subjects reporting these symptoms in the booster stage generally lower than those reporting them after any dose following the primary series. Severe systemic events were reported by ≤3.7% of subjects across study groups, and antipyretic medication was used by ≤13.0% of subjects across study groups. The median duration of systemic events after booster vaccination was 1–3 days across study groups. Few subjects (≤3 in each study group per type of systemic event) reported a severity increase with potentiation for any systemic event. No subjects withdrew from the study due to systemic events.

Percentages of subjects reporting AEs, immediate AEs, SAEs, NDCMCs, and MAEs throughout the booster stage are shown in Table 2. Overall, 3.7–12.5% of subjects depending on study group reported AEs during the booster stage. Two reported AEs were evaluated as being possibly related to the investigational product: one subject in the 0-, 6-month study group with mild worsening of psoriasis 5 days after receipt of booster vaccination and another subject in the 0-, 2-month study group with a severe influenza-like illness 2 days after booster vaccination (an SAE), which resolved after 10 days. No immediate AEs were reported, and no

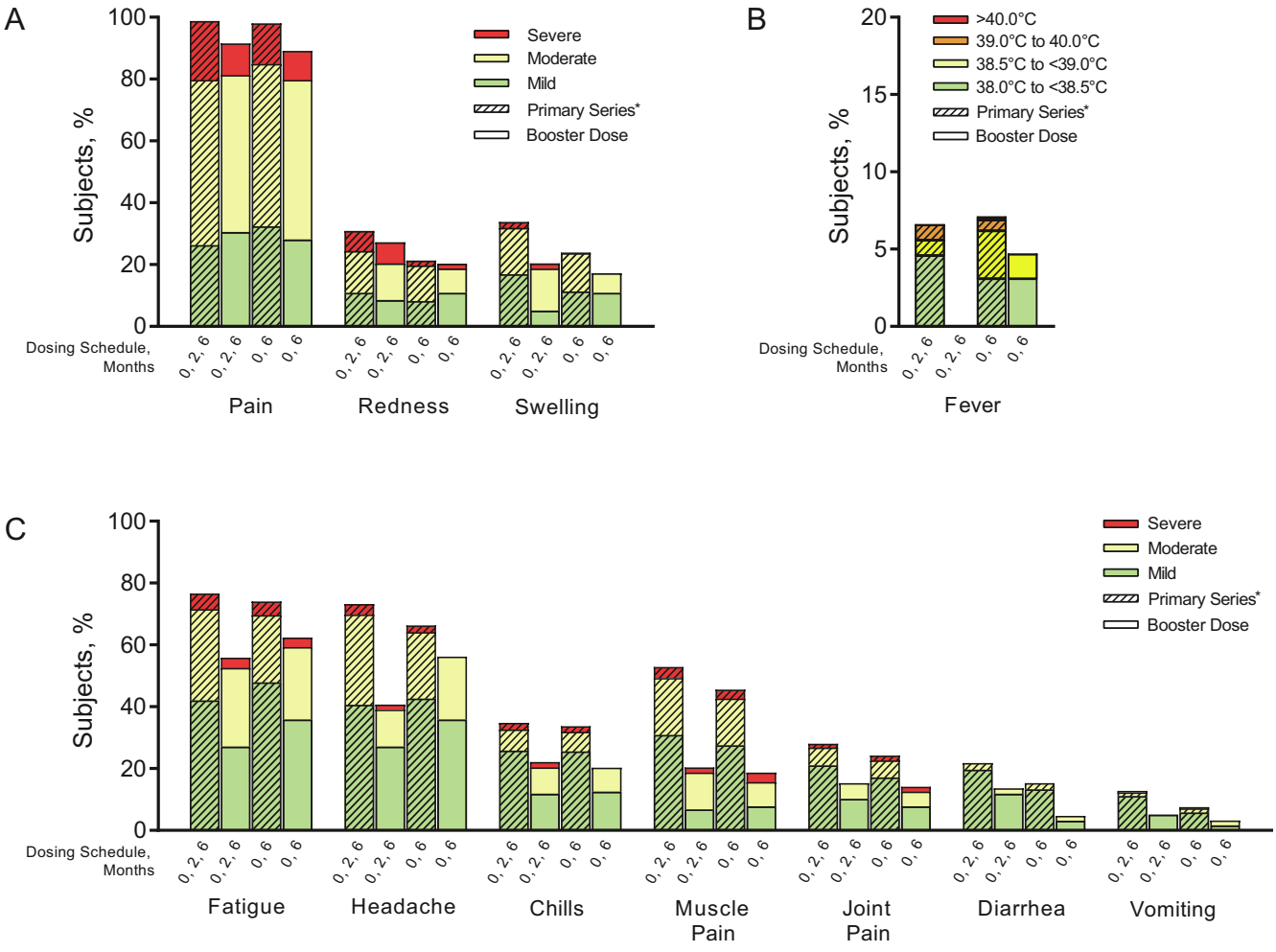

Fig. 4. Percentages of subjects reporting (A) local reactions, (B) fever, and (C) systemic events within 7 days after any dose of the primary series or the booster dose. Only the 0-, 2-, 6-month and 0-, 6-month study groups are shown for simplicity. *Reaction after any dose of the primary series.

Table 2
AEs, immediate AEs, SAEs, NDCMCs, and MAEs reported during the booster stage.

Event	0-, 1-, 6- Month Schedule (N = 59)* n (%)†	0-, 2-, 6- Month Schedule (N = 59)* n (%)†	0-, 6-Month Schedule (N = 64)*, n (%)†	0-, 2-Month Schedule (N = 54)* n (%)†	0-, 4-Month Schedule (N = 32)* n (%)†
AE‡	4 (6.8)	6 (10.2)	8 (12.5)	2 (3.7)	3 (9.4)
Related	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.9)	0 (0.0)
Leading to withdrawal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Immediate AE§	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAE‡	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.9)	0 (0.0)
Related	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)
NDCMC‡	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
MAE‡	3 (5.1)	4 (6.8)	3 (4.7)	0 (0.0)	0 (0.0)
Related	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AE = adverse event; MAE = medically attended adverse event; NDCMC = newly diagnosed chronic medical condition; SAE = serious adverse event.
* Number of subjects in the safety population.
† Subjects with at least one event.
‡ During booster vaccination phase = from booster vaccination through 1 month after booster vaccination.
§ Immediate AE = AE occurring within 30 min of vaccination.

subjects reported NDCMCs during the booster stage. SAEs were reported by two subjects and included a meniscus injury and the severe influenza-like illness described above; only the latter was deemed related to the investigational product.

Among subjects reporting AEs, 37.5–100.0% reported missing a median of 2–10 days of school or work as a result. Missed days of school or work were reported in connection with one related AE, in which a subject missed 2 days of school or work due to the severe influenza-like illness described above.

5. Discussion

This was the first study to evaluate immune response persistence after both two- and three-dose primary schedules of MenB-FHbp and to assess safety and immunogenicity of a booster dose given 48 months after the primary vaccination series. Safety and immunogenicity after the primary series have been previously reported [20]. Results from the persistence stage of the current study suggest that immune responses decline during the first 12 months after the primary series and then plateau through 48 months. At the 48-month time point, 24.0–61.6% of subjects maintained protective titers (ie, ≥1:4) compared with 7.1–28.9% of subjects before vaccination in the primary study, demonstrating that for many individuals, vaccination can continue to provide protection for ≥4 years regardless of whether a two- or three-dose primary schedule was received.

The robust immune responses to a booster dose given at the 48-month time point were indicative of immunologic memory: after the booster dose, 91.9–100.0% of subjects had hSBA titers ≥LLOQ against the four test strains, with a high proportion of subjects demonstrating a protective response against all four strains; GMTs after the booster dose were also higher than after the primary series. These responses were observed regardless of whether a two- or three-dose primary schedule was received.

A booster dose was generally safe and well-tolerated in this population. Local and systemic reactions after the MenB-FHbp booster dose were generally reported less frequently than those after any dose in the corresponding primary study. There were few reported SAEs and MAEs, with only one SAE (influenza-like illness) considered related to MenB-FHbp.

A recently published phase 2 study by Marshall et al reported immunologic persistence of MenB-FHbp vaccination among individuals 11–18 years of age at the time of study entry who received primary doses at 0, 2, and 6 months [28]. Percentages of subjects achieving hSBA ≥LLOQ at 48 months after primary vaccination ranged from 51.1–59.0% for MenB test strains expressing FHbp variants A22, A56, and B24, whereas 20.4% of subjects had hSBA ≥LLOQ for the test strain expressing variant B44. The study by Marshall et al and the current study found that antibody levels declined similarly during the 12 months after primary vaccination; however, the current study also importantly demonstrated robust immune responses to a booster dose given approximately 48 months after primary series completion.

In the current study, the 0-, 6-month MenB-FHbp primary series schedule had the longest interval (ie, 6 months) between doses 1 and 2 among the two-dose study groups evaluated in the primary study [20]. The demonstration of robust immune responses for subjects in this study group [20] contributed to US and EU approval of a two-dose regimen under this schedule [12,13]. The current study further supports use of a 0-, 6-month primary schedule by demonstrating that under this schedule, immunologic persistence and immune responses to a booster dose are similar to those under three-dose primary schedules. Schedule choice may be influenced by an individual's susceptibility to MenB IMD, with a three-dose schedule preferred for those at increased risk (eg, due to an outbreak or a specific medical condition) given the protective response induced by two initial doses given in rapid succession which is then augmented by a third dose; a 0-, 6-month schedule may apply to individuals not considered to be at increased risk [13].

The current study has some limitations. Sample sizes were smaller than sample sizes in some phase 3 studies but were larger than sample sizes in some other persistence and booster studies for the other available protein-based MenB vaccine [29,30]. However, immune responses were consistent across study groups and consistent with those achieved in the earlier persistence study by Marshall et al [28]. Forthcoming persistence and/or booster data for subjects from the two other primary studies [22,31], which included subjects from other geographic regions, will further supplement the current data. An additional limitation is that hSBA responses were used as a surrogate for efficacy (efficacy studies would be impractical because of the low incidence of MenB disease); however, this approach has been supported by postlicensure studies for other meningococcal vaccines [26,27]. Third, only 4 MenB strains were tested for immunogenicity determination; however, these test strains are considered representative of diverse MenB disease-causing strains and have demonstrated predictive value of response to a broader set of 10 additional MenB test strains in 2 pivotal phase 3 studies [21,24]. Fourth, immunogenicity data were not available for time points between 1 and 12 months following primary vaccination; variations in persistence between groups during this period may be important. Additionally, the booster dose was only evaluated when given at one time point (4 years). Finally, as noted, this interim report provides safety and immunogenicity data for 1 month after the MenB-FHbp booster dose; forthcoming data on the persistence of the postbooster response will further inform guidelines on the use of a booster dose.

Broadly protective responses following receipt of a booster dose suggest that booster vaccination may help extend protection throughout the period of risk. Importantly, booster dose immune responses measured in the current study were indicative of immunologic memory, and were similar regardless of whether a two- or three-dose primary series schedule was received.

Author contributions

All authors contributed to data analysis or data interpretation, contributed substantially to the preparation and editing of the manuscript, and approved the final version for submission.

Declaration of interests

TV and LØ report grants from Pfizer Inc during the conduct of the study. JB, SLH, and JP report personal fees from Pfizer Inc during the conduct of the study, and additionally have a patent US Patent 9561269 issued, and a patent US20150071959 pending. All other authors report personal fees from Pfizer Inc during the conduct of the study.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2018.11.073.

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