

## Bexsero®: A New Vaccine Approved For Serogroup B *Neisseria Meningitidis*

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The incidence of meningococcal disease in the United States ranges from 800 to 1,500 cases annually and of these, approximately 12% derive from bacterial etiologies, namely *Neisseria meningitidis* in the United States.<sup>1</sup> Although meningococcal disease is treatable, it claims the lives of ~10% to 15% of patients afflicted.<sup>3</sup> Of those who survive meningococcal disease, 10% to 20% will end up with long term disabilities including hearing loss, brain damage, amputations and severe scarring from skin grafts.<sup>2</sup>

There are at least 12 serogroups of *N. meningitidis*. The most common serogroups to cause harm to humans include serogroups A, B, C, W and Y.<sup>1</sup> In children aged five years and younger, serogroup B is the cause of approximately 60% of meningococcal cases.<sup>3</sup> In people aged  $\geq 11$  years, serogroups C, W and Y are responsible for 73% of meningococcal disease.<sup>3</sup> Currently available meningococcal vaccinations only cover a combination of serogroups A, C, W and Y. Creating a vaccine to cover serogroup B have proven difficult due to the similarities between the serogroup B capsular polysaccharide and the human polysialic acid.<sup>4</sup> There are also multiple disease-causing strains of serogroup B, making it difficult to pinpoint a universal antigen for a vaccine to target. Nevertheless, on January 23<sup>rd</sup>, 2015, Bexsero®, also known as 4CMenB, received an FDA-approved indication for prevention of invasive meningococcal disease caused by *N. meningitidis* serogroup B in individuals 10 through 25 years of age. The purpose of this article is to highlight and summarize three clinical trials evaluating the effectiveness of Bexsero®, the adverse effects and precautions, the dosing and administration, and the costs of this new vaccine.

### CLINICAL PHARMACOLOGY

Proteins found on the surface of the meningococci contribute to the bacteria's ability to cause disease. Proteins including

neisseria heparin binding protein (NHBA), neisserial adhesion (NadA), factor H binding protein (fHbp) and outer membrane vesicles (PorA) have been found to contribute to the serogroup B disease.<sup>4</sup> NadA is involved in host cell adhesion in the nasopharyngeal epithelium to cause invasion. NHBA has the ability to bind to heparin which may lead to serum resistance. Binding to human factor H-binding protein may enhance serum resistance. Bexsero® was designed using a novel reverse vaccinology approach to identify these subcapsular surface antigens that were common to many serogroup B strains.<sup>4</sup> In contrast, Trumenba®, another serogroup B vaccine, was designed using two recombinant lipidated fHbp variants. By including the recombinant forms of the fHbp, NHBA, NadA, and Por A, Bexsero® allows the body to create antibodies against certain strains of serogroup B meningococcal disease.

### CLINICAL TRIALS

Three trials have evaluated immunologic response to Bexsero®. In general, these trials have been relatively small, enrolling pediatric and adolescent patients, and assessing surrogate outcomes – that is, the percentage of subjects reaching pre-specified thresholds for a serum bactericidal assay (hSBA) titre level after a series of 4CMenB against placebo injections. A  $\geq 4$  titre level has been shown to have protective effects against meningococcal disease. As discussed below, one trial also assessed long-term antibody persistence. These trials are summarized in **Table 1**. To date, no trials have assessed long-term clinical outcomes (i.e., infection rates or major events such as hospitalization or death).

Santolaya and colleagues performed a randomized, observer-blinded, placebo-controlled phase 2b/3 trial in 12 sites across Chile over a 2-year period.<sup>5</sup> Subjects were eligible for this study if they were healthy adolescents, of either sex, aged 11 to 17 years, with no previous history of meningococcal serogroup B vaccine or meningococcal disease. Exclusion criteria included allergy to any component of the vaccine, any household contact with a confirmed case of meningococcal disease within 60 days, any immunization within 30 days (except for the influenza vaccine), receipt of antibiotics within 6 days or blood products or any investigational product within 90 days of enrollment. Subjects were randomly allocated into five groups: a single vaccine dose (n=375); two vaccine doses, one month apart (n=375); two vaccine doses, two months apart (n=380); three vaccine doses, one month apart (n=373); or, placebo (n=128). Each group received three injections over the course of three consecutive months.

The primary endpoint of this study was the percentage of subjects with protective hSBA titre of  $\geq 4$ . Baseline characteristics between groups were similar with a mean age ranging from 13.7 to 13.9 years. Approximately 52% to 59% of subjects were female, and Hispanics made up 99% to 100% of subjects. At baseline, 44% of the participants had  $\geq 4$  titres to fHbp, 34% had  $\geq 4$  titres to NadA, and 35% had  $\geq 4$  titres for the outer membrane vesicle.



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**Table 1 | Summary of clinical trials for Bexsero®**

Trial	Santolaya, et al. <sup>5</sup>	Lee, et al. <sup>6</sup>	McQuaid, et al. <sup>9</sup>
<b>Patient Population</b>	Age 11-17 years	Age 11-17 years	Age ≤5 years
<b>Treatments</b>	<ul style="list-style-type: none"> <li>• One 4CMenB (n=375)</li> <li>• Two 4CMenB 1 month apart (n=375)</li> <li>• Two 4CMenB 2 months apart (n=380)</li> <li>• Three 4CMenB 1 month apart (n=373)</li> <li>• Three placebo (n=128)</li> </ul>	<ul style="list-style-type: none"> <li>• Two 4CMenB one month apart (n=170)</li> <li>• One placebo dose followed by one Menveo® (n=88)</li> </ul>	<ul style="list-style-type: none"> <li>• 4CMenB group from a previous trial were assessed for titre levels at 60 months of age</li> <li>• 4CMenB-naive 5 year olds received 2 doses at 60 and 62 months</li> </ul>
<b>Endpoints</b>	<ul style="list-style-type: none"> <li>• Primary: % of subjects with protective hSBA titre of ≥ 4</li> </ul>	<ul style="list-style-type: none"> <li>• Primary: % of subjects with protective hSBA titre of ≥ 4 1 month after 2<sup>nd</sup> dose</li> </ul>	<ul style="list-style-type: none"> <li>• Primary: to assess the persistence of antibodies at 40 months of age, as previously reported</li> <li>• Secondary: immunogenicity, safety and tolerability of a 2-dose catch-up regimen of 4C-MenB vaccine administered at 60 and 62 months</li> </ul>
<b>Results</b>	Over 90% of participants developed protective hSBA titres after 1 dose. After 2 doses, 99-100% developed protective hSBA titres	One month after the second dose, subjects achieved 93%, 97%, and 83% against fHbp, NadA, and PorA	<p>Antibody titers were observed to be waning in participants who were vaccinated as infants. The extent of the decrease varied by strain.</p> <p>Catch-up regimen were observed to have 92%-100% hSBA titres for all strains</p>

**fHbp**= factor H binding protein; **hSBA**= serum bactericidal assay; **NadA**= nesserial adhesion A; **PorA**= outer membrane vesicles

After one dose of Bexsero®, 93% of participants had ≥4 titres for fHbp, 96% to NadA, and 93% to outer membrane vesicles. After a second dose, greater than 99% of participants had ≥4 titres to fHbp, NadA, and outer membrane protein (p<0.0001 compared with one dose). Greater than 99% of subjects who received 2 to 3 doses of the vaccine had titre levels ≥4 (p<0.0145 compared to one dose). A third dose did not appear to significantly increase titre levels (p=0.176). There was no suitable strain to assess the bactericidal responses against NHBA at the time of testing. To counteract this, samples from each group were tested by ELISA for antibodies to this antigen. NHBA antigen ELISA concentrations had a similar response pattern to titres against other antigens, low concentrations of antigens at baseline, with a substantial increase one month after the first dose. Titres were boosted by an order of magnitude with a second dose, however, a third dose only elicited a small increase.

Lee and colleagues performed a randomized, observer-blinded, study at multiple sites across Korea over a seven month period.<sup>6</sup> Subjects were eligible for this study if they were healthy adolescents, of either sex, aged 11 to 17 years. Subjects were excluded if they had a history of meningococcal vaccination or suspected/confirmed diagnosis of meningococcal disease, house contact with an individual with confirmed meningococcal infection within 60 days of enrolment, any serious chronic or progressive disease, impairment of the immune system, use of immuno-

suppressants, use of immunostimulants within the previous 90 days or a history of serious reaction to any component of the vaccine. Subjects meeting the inclusion criteria were randomly assigned in a 2:1 ratio to receive two doses of Bexsero® or one placebo dose and one dose of Menveo®, a vaccine indicated for prevention of meningococcal serogroups A, C, Y and W.

The primary endpoint of this study was to assess the immunogenicity of Bexsero® when given as two doses by measuring the percentage of subjects with a serum titre level of ≥4, one month after the second dose. Serum bacterial assay titres were obtained prior to the first vaccination and one month after the second vaccination. Baseline demographics and titre levels were similar in both groups. Baseline mean age was 13.5 and 13.4 years in the Bexsero® and control groups, respectively. Roughly 56% and 59% of the subjects were male in the control and placebo groups, respectively, and 100% of enrolled patients were Asian.

One month after the second dose was given, the percentage of subjects achieving ≥4 titre levels in the 4CMenB group was 97% (95% CI: 93% to 99%) against NadA and PorA test strains, and 98% (95% CI: 94% to 99%) against fHbp. One month after the second dose, the placebo group achieved serum titre levels of ≥4 in 16% (95% CI: 9% to 25%) against NadA, 17% (95% CI: 10% to 27%) against PorA, and 27% (95% CI: 15% to 34%) against fHbp. The 4CMenB vaccine was shown to be more immunogenic in this study when compared to the control vaccines.<sup>6</sup>

A series of three studies were conducted by following infants administered with Bexsero® to measure the percentage of subjects with serum titre level ≥ 4 and to measure the persistence of specific bacterial antibodies over time. The original study, led by Findlow and colleagues was comprised of 147 infants from the United Kingdom.<sup>7</sup> Subjects in the original study were randomly allocated to four groups: four doses of Bexsero® (n=46), four doses of Trumenba® (n=46), one dose of Bexsero® (n=23), or one dose of Trumenba® (n=23). Baseline characteristics in the original study were similar between groups: mean age was 59 to 61 days, 52% to 54% of patients in the three-dose series were boys, whereas in the single dose arms, 61% and 17% were boys. The majority of the infants were white. After three doses of Bexsero® and Trumenba®, both vaccines showed increased percentages of subjects with serum titre levels ≥ 4 against NadA and fHBP. A greater increase in immunogenicity against PorA was demonstrated in the Bexsero® group. After the fourth dose, both groups elicited anamnestic responses. In the single dose group, both vaccines demonstrated poorer immunogenicity responses when compared to the multi-dose groups.

Snape and colleagues continued this work with a 40-month extension study.<sup>8</sup> Subjects (from the aforementioned U.K. study) with four doses of Bexsero® (n=19) or Trumenba® (n=29) were given another dose of the same vaccine at 40 months. Subjects previously allocated into the single dose of Bexsero® (n=8) or Trumenba® (n=14) groups received one additional dose of the same vaccine at 40 months and another at 42 months. A fifth vaccine-naive group (n=43; not a part of the aforementioned U.K. study) received Bexsero® at 40 and 42 months. Waning of antibodies from the original study groups were observed at baseline. Following the administration of booster doses in each respective group, anamnestic responses were observed. After receiving Bexsero® at 40 and 42 months in the vaccine-naive group, the percentage of subjects with serum titre level ≥ 4 increased compared to baseline.

McQuaid continued the study on the persistence of specific bacterial antibodies at five years of age.<sup>9</sup> Subjects were included in the study if they participated in the aforementioned 40-month extension study by Snape and colleagues.<sup>8</sup> All the subjects that participated in the 40 month extension study were invited back for this extension study once they reached 60 months of age. Subjects from the extension study were not re-vaccinated at 60 months. Along with the original participants (n=105), 50 healthy, vaccine-naive controls were recruited by mail. Exclusion criteria for the vaccine-naive group included any previous history of meningococcal vaccination or a history of meningococcal disease, severe allergy to any component of the vaccine, and any serious chronic or progressive disease or suspected immune system impairment. Receiving any other vaccine within 30 days before or

**Table 2 | Adverse drug reactions in the Bexsero®- and placebo-treated patients.<sup>5</sup>**

Adverse reaction	Bexsero (N=3330 doses)	Placebo (N=2739)
Pain	86%	60%
Severe pain	17%	4%
Malaise	51%	30%
Headache	42%	27%
Fever (Temp ≥ 38°C)	4%	2%

after the meningococcal vaccine was not permitted, unless it was the influenza vaccine. Subjects in both groups had a single 5-ml blood sample drawn at 60 months. The vaccine-naive control group received one dose of Bexsero® at 60 months and another at 62 months of age. Another blood sample was taken one month after the second dose in the control group.

The primary endpoint of this study was to assess the persistence of antibodies in subjects at 60 month, compared with their previously reported levels at 40 months. Overall, there were 163 participants enrolled in this study, including 79 boys and 84 girls. The majority of the subjects were white (n=152) and aged 59 to 63 months. At 60 months of age, subjects from the 40-month extension study saw decreased protective antibody titre levels against 4 indicator strains of serogroup B meningococcus that were matched to each individual vaccine component, and 4 mismatched strains. The decrease in Bexsero® and Trumenba® groups were similar, except that no hSBA response against the outer membrane vesicle component was observed at 60 months for Trumenba®. This result was expected due to the properties of Trumenba®, which does not contain PorA, a protein from the outer membrane vesicle. Administration of Bexsero® in the vaccine-naive group demonstrated protective titre levels against 92% to 100% in both matched and mismatched strains, with a notable exception of 59% in one mismatched strain. As a catch-up course, this study demonstrated that Bexsero® was immunogenic when given to children at 60 months of age, however, the persistence of immunity later in childhood is unknown.

**ADVERSE EVENTS AND PRECAUTIONS**

Table 2 lists the common side effects associated with Bexsero® seen during clinical trials. Pain at the injection site was significantly more common with Bexsero® when compared with placebo. Other common reactions include malaise, headache, and

**Table 3 | Current CDC Vaccine Price List<sup>13</sup>**

Vaccine (serogroup coverage)	Brand Name	CDC Cost/Dose	Private Sector Cost/Dose	Manufacturer
Meningococcal Group B	Bexsero®	\$122.95	\$160.75	GlaxoSmithKline
Meningococcal Group B	Trumenba®	\$95.75	\$115.75	Pfizer
Meningococcal Conjugate (A,C,W,Y)	Menveo®	\$83.56	\$117.42	GlaxoSmithKline
Meningococcal Conjugate (A,C,W,Y)	Menactra®	\$84.95	\$112.93	Sanofi Pasteur

fever.<sup>6</sup> The package insert also lists myalgia ( $\geq 48\%$ ), erythema ( $\geq 45\%$ ), fatigue ( $\geq 35\%$ ), induration ( $\geq 28\%$ ), nausea ( $\geq 18\%$ ), and arthralgia ( $\geq 13\%$ ) as other commonly reported adverse reactions.

Contraindications to Bexsero<sup>®</sup> include severe or life threatening allergies to any part of the vaccine.<sup>4</sup> Patients with latex allergy should not use this vaccine. Precautions and warnings listed by the manufacturer include syncope, altered immunocompetence, allergic reactions and latex.<sup>4</sup> Health care providers should be aware of these precautions and have interventions in place to counteract them should they arise.

Pregnant women have not been studied in clinical trials of Bexsero<sup>®</sup>. Animal studies suggest no impairment of fertility or fetal harm. Nevertheless, Bexsero<sup>®</sup> should only be used in pregnancy when it is clearly needed. It is currently unknown if this vaccine is excreted in human milk. Caution should be used when administering Bexsero<sup>®</sup> to nursing mothers. The safety and effectiveness of Bexsero<sup>®</sup> in patients aged  $\leq 10$  or  $\geq 65$  years have not been established. Vaccine-drug interactions or vaccine-vaccine interactions with Bexsero<sup>®</sup> have not been identified to date. Further clinical trials are required to establish these interactions.

### DOSING AND ADMINISTRATION

Bexsero<sup>®</sup> is administered intramuscularly via a 0.5-mL pre-filled syringe. Each vial of Bexsero<sup>®</sup> contains 50 micrograms of NadA, NHBA, and fHbp, 25 micrograms of outer membrane vehicle, 1.5 mg aluminum hydroxide, 3.125 mg sodium chloride, 0.776 mg histidine and 10 mg of sucrose contained in a 6.4 to 6.7 pH solution.<sup>4</sup> Bexsero<sup>®</sup> should be administered into the deltoid region of the upper arm. This vaccine is scheduled as a two-step vaccine, given one month apart.<sup>2,4</sup> Bexsero<sup>®</sup> is approved for use in patients aged 10 to 25 years who are at increased risk of contracting serogroup B meningococcal disease. Individuals at increased risk include patients near a serogroup B disease outbreak, individuals with their spleen removed, individuals with persistent complement component deficiency, individuals taking eculizumab (Soliris), or microbiologists who work with *N. meningitidis* isolates.<sup>2</sup> Prior to administration of the vaccine, the syringe should be shaken to create a homogenous solution and visually inspected for particulate matter or discoloration. If particulate matter or discoloration are found, the product should not be used and should be discarded.

### COST

Table 3 lists the cost of Bexsero<sup>®</sup> and other vaccines that protect against meningococcal disease. Trumenba<sup>®</sup> may be given as a two or three dose schedule.<sup>10</sup> Menveo<sup>®</sup> has a single dose, a two dose series, or a four dose series, with the appropriate administration series dependent on age.<sup>11</sup> Menactra<sup>®</sup> has two dosing schedules, depending on age: it may be given as a single dose or a double dose.<sup>12</sup>

### SUMMARY

Bexsero<sup>®</sup> is a new serogroup B meningococcal vaccine, designed to protect against the strain of *N. meningitidis* that previously had no vaccine. Clinical trials have shown significant increases in the percentage subjects with protective hSBA titres of  $\geq 4$ . However, trials have shown that these titre levels wane over time and the effectiveness in reducing the rates of meningococcal infection is currently unknown. Due to this vaccine being new to

the market, pricing may be an issue when compared to other meningococcal vaccines. Additional information will be needed to determine Bexsero's<sup>®</sup> place on the vaccination schedule. Pricing, uncertainty in preventing disease, and waning titre levels make it indicated for certain at risk populations.

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