1 **Immune responses to a recombinant, four-component, meningococcal serogroup**
2 **B vaccine (4CMenB) in adolescents: A phase III, randomized, multicentre, lot-to-**
3 **lot consistency study**

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33 **Short title:** MenB vaccine kinetics in adolescents
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93 **Abstract:**

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95 **Background:** For decades, a broadly effective vaccine against serogroup B *Neisseria*

96 *meningitidis* (MenB) has remained elusive. Recently, a four-component recombinant

97 vaccine (4CMenB) has been developed and is now approved in Europe, Canada,

98 Australia and some Latin American countries. This phase III, randomized study

99 evaluated the lot consistency, early immune responses and the safety profile of

100 4CMenB in 11 to 17-year-old adolescents in Australia and Canada (NCT01423084).

101

102 **Methods:** In total, 344 adolescents received two doses of one of 2 lots of 4CMenB, 1-

103 month apart. Immunogenicity was assessed before, 2-weeks and 1-month following

104 the second vaccination. Serum bactericidal activity using human complement (hSBA)

105 was measured against three reference strains specific for the vaccine antigens

106 Neisseria adhesin A (NadA), factor H binding protein (fHbp) and porin A (PorA)

107 containing outer membrane vesicle (OMV). Responses to the Neisseria heparin

108 binding antigen (NHBA) were assessed with an enzyme linked immunosorbent assay

109 (ELISA). Local and systemic reactions were recorded for 7 days after each

110 vaccination; unsolicited adverse events were monitored throughout the study. .

111

112 **Results:** Immunological equivalence of the two lots of 4CMenB was established at

113 1-month after second vaccination. At baseline, ≤7% of participants had hSBA titres

114 ≥5 to all the three reference strains. Two weeks following the second dose of

115 4CMenB, all participants had hSBA titres ≥5 against fHbp and NadA compared with

116 84–96% against the PorA antigens. At 1-month, corresponding proportions were 99%,

117 100% and 70–79%, respectively. Both lots were generally well tolerated and had

118 similar adverse event profiles.

119

120   **Conclusions:** Two doses of 4CMenB had an acceptable safety profile and induced a

121   robust immune response in adolescents with peak antibody responses observed at 14

122   days after vaccination. While a substantial non-uniform antigen-dependent early

123   decline in antibody titers was seen thereafter, a significant percentage of participants

124   continued to maintain protective hSBA titers at 1-month.

125

126   **Funding:** Novartis Vaccines

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128   **Word Count = 302**

129 **Introduction**

130 Over the last two decades, substantial progress has been made in reducing the burden

131 of disease caused by *Neisseria meningitidis* through vaccination. Successful mono-

132 and multivalent vaccines against serogroups A, C, W and Y have been developed

133 based on serogroup-specific capsular polysaccharides and enhanced with

134 polysaccharide-protein conjugate technology. However, this vaccine strategy cannot

135 be employed for serogroup B, the last of the five major pathogenic meningococcal

136 groups, due to the capsule's structural homology to human fetal neural tissues,

137 resulting in poor immunogenicity [1, 2]. Serogroup B *Neisseria meningitidis* (MenB)

138 is now the leading cause of meningococcal disease in infants and young children,

139 accounting for over 80% of cases in Australia and some Latin American countries,

140 over 70% in Europe, 66% in the UK, 50-80% in Canada and one-third in the USA [3-

141 7].

142

143 Previously, tailor-made MenB vaccines have been developed from strain-specific

144 outer membrane vesicles (OMV) and successfully used to combat homologous strains

145 in clonal outbreaks [8-11]. However, due to limited or no effectiveness against

146 heterologous strains they are not suitable for use as a general serogroup B vaccine

147 [12]. Recently however, important advances have been made in the quest for a

148 universal MenB vaccine with the identification of conserved sub-capsular

149 meningococcal proteins [13, 14].

150

151 One four-component recombinant vaccine, 4CMenB, contains three recombinant

152 proteins: factor H binding protein (fHbp), Neisserial adhesin A (NadA) protein and

153 Neisseria heparin binding antigen (NHBA), along with porin A (PorA) containing

154   OMV derived from meningococcal NZ98/254 strain (previously used to control a

155   MenB clonal outbreak in New Zealand (NZ), the main PorA antigen is P1.4) [15].

156   Since development, the 4CMenB vaccine has been administered in phase I, and

157   pivotal phase IIb and III studies to over 8000 adults, adolescents and infants and has

158   been shown to be immunogenic, as measured by serum bactericidal assay using

159   human complement (hSBA), to a majority of reference strains within hypervirulent

160   clusters responsible for MenB disease [16-18].

161

162   This study measured baseline immunity, and the consistency and kinetics of immune

163   response following a two-dose schedule of two lots of 4CMenB (manufactured at

164   different sites) in healthy Australian and Canadian adolescents. Safety and tolerability

165   were also assessed.

166

167 **Methods**

168 **Study design and participants**

169 The study (NCT01423084) was a phase III, multicentre, observer-blind, randomized

170 trial which involved healthy 11 to 17-year-old adolescents across five centres in

171 Australia and seven in Canada between August and December 2011. Potential

172 participants were identified via advertising fliers in school newsletters or on

173 community noticeboards and from participant databases at the research centres.

174 Exclusion criteria were: previous receipt of MenB vaccine; previous meningococcal

175 disease (or household or intimate contact with an individual with *N. meningitidis*);

176 recent significant acute or chronic infection or fever ≥38.0°C; recent antibiotic use;

177 known immunodeficiency or use of immunosuppressive doses of corticosteroids;

178 recent receipt of any blood products including immunoglobulin, planned receipt of

179 other vaccines within 30 days (within 14 and 60 days for influenza and live viral

180 vaccines respectively) or allergy to vaccine components. Participants were also

181 excluded if they were pregnant, breast feeding or unwilling to use acceptable birth

182 control measures within 30 days prior and 60 days following enrolment. A negative

183 pregnancy test was required for all females prior to receipt of each dose of 4CMenB

184 vaccine. Written assent was obtained from each adolescent and written informed

185 consent was obtained from participant's parents or legal guardians. Approvals were

186 obtained from ethics committees at each participating research centre.

187

188 Both lots of the investigational vaccine 4CMenB had identical composition but were

189 formulated with OMV manufactured by Novartis Vaccines at two different sites in

190 Italy: Rosia (Lot 1) and Siena (Lot 2).

191

192   Participants were randomized in a 1:1 ratio to receive two doses of either Lot 1 or Lot

193   2 of 4CMenB vaccine, one month apart. Blood samples (maximum 20 mL) were

194   taken on day 1 before the first vaccination and 30 days after the second vaccination.

195   At pre-selected sites, an extra blood sample was taken two weeks following the

196   second dose in all participants to investigate the kinetics of the early immune response

197   after vaccination (Table 2). Participants were observed for at least 30 minutes after

198   each study vaccination. Local and systemic reactions and adverse events (AE) were

199   collected on a diary card for seven days following each vaccination. Serious adverse

200   events (SAE), medically attended AEs and AEs that resulted in a participant's

201   withdrawal from the study were collected throughout the study period.

202

203   **Serological responses**

204   Assays were performed at the Clinical Laboratory Science, Novartis Vaccines

205   Marburg, Germany. Sera were tested for bactericidal activity using a human

206   complement source (hSBA), against each of the three *N. meningitidis* serogroup B

207   reference strains: 44/76-SL (fHbp), 5/99 (NadA) and NZ98/254 (PorA) using the

208   method described previously ( ). These strains were chosen as each is mismatched for

209   all but one of the vaccine antigens, therefore each strain assesses the response to a

210   single vaccine component (44/76-SL - fHbp, 5/99- NadA and NZ98/254-PorA). The

211   IgG antibody concentration to the NHBA antigen were assessed using an enzyme-

212   linked immunosorbent assay (ELISA). At the time of the study, no suitable strain for

213   NHBA responses had been identified therefore an NHBA-specific ELISA was used

214   against vaccine antigen 287-953 ( ).

215

216   **Statistical analysis**

217   The primary objective was to demonstrate equivalence of Lot 1 to Lot 2 of 4CMenB,

218   as measured by hSBA geometric mean titre (GMT) against 3 reference strains (44/76-

219   SL, 5/99 and NZ98/254) and ELISA geometric mean concentration (GMC) IgG

220   against the NHBA, 30 days after a primary course of 2 doses administered one month

221   apart. Equivalence was defined as the two-sided 95% confidence interval (CI) of the

222   ratio of the hSBA GMTs and GMCs being contained within the interval (0.5, 2.0).

223   The primary safety objective was to evaluate the safety and tolerability of two doses

224   of two lots of 4CMenB given one month apart in healthy adolescents.

225

226   The secondary immunogenicity objectives were to: assess the increase in hSBA GMT

227   and ELISA GMC (post- to pre-vaccination); and to calculate the percentage of

228   participants in each lot with hSBA $\geq$ 1:5 one month following the second vaccination

229   for each of the three reference strains (44/76-SL, 5/99 and NZ98/254). Further, in a

230   subset of approximately 160 participants (80 per lot), the same outcome measures

231   were assessed two weeks following the second vaccination.

232

233   For each lot and each reference strain and for the NHBA antigen, the GMT (or GMC)

234   and two-sided 95% CI was calculated. These were obtained from a two-way analysis

235   of variance (ANOVA) with factors for vaccine lot and study centre. For the

236   percentage of subjects with hSBA $\geq$ 1:5, the associated 95% Clopper-Pearson

237   confidence interval (CI) was measured. No between-group comparisons were

238   performed for any immune measure besides the primary endpoint, because the

239   analysis was underpowered to demonstrate equivalence. Titres and concentrations

240   below the limit of detection (2 for hSBA and 40 for ELISA) were set to half that limit

241   (i.e: 1 for hSBA and 20 for ELISA) for the purpose of analysis.

242

243   The planned sample size of 135 evaluable participants (160 minus 15% attrition) per

244   arm, was calculated to provide 94% overall power to demonstrate consistency of the

245   immune response to the two lots of 4CMenB assuming a two-sided $\alpha = 0.05$, an

246   underlying ratio of the vaccine group GMTs or GMCs of 1.0 for each of the reference

247   strains, and an equivalence interval of (0.5, 2.0). For an underlying ratio of the

248   vaccine group GMTs (or GMCs) of 1.1 for each strain, the overall power to

249   demonstrate consistency was calculated as approximately 90%.

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262 **Results**

263 Of the 344 participants enrolled into the study, 170 were included in Lot 1 (Rosia)

264 and 174 in Lot 2 (Siena) of whom 99% and 98% of participants completed the study,

265 respectively. The per-protocol immunogenicity population (299 participants) included

266 adolescents with no major protocol violations who provided sera for testing (147 and

267 152 participants from Lot 1 and 2, respectively) (Figure 1). The safety population

268 comprised 342 participants (169 participants from Lot 1 and 173 from Lot 2). The

269 demographic and baseline characteristics were well matched except for gender. The

270 mean age at enrolment was 13.7 years [± 1.9] (Table 1). The per protocol population

271 for the extra blood taken two weeks following the second vaccination (visit 2)

272 consisted of 76 and 71 participants in Lot 1 and 2, respectively.

273

274 At baseline, of 299 participants, 6 (2%) had hSBA titres ≥ 5 to the reference strains

275 for fHbp (44/76-SL), 20 (7%) for NadA (5/99) and 5 (2%) for PorA (NZ98/254).

276

277 **Primary objective**

278 One month following the second vaccination, the ratios of hSBA GMTs in Lot 1 to

279 Lot 2 were 1.0, 0.92 and 0.81 for each of the 3 reference strains 44/76-SL, 5/99 and

280 NZ98/254 respectively, with corresponding CI of (0.82, 1.23), (0.77, 1.1) and (0.6,

281 1.09) (Table 2). The Lot 1 to Lot 2 ratio of the ELISA GMCs against the NHBA, one

282 month following the second vaccination, was 0.83 (95% CI: 0.67, 1.02) (Table 2).

283 Statistical equivalence of the two vaccine lots was met, as each ratio and CI were

284 contained within the interval 0.5 and 2.0.

285

286 **Secondary objectives**
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288 **Immune response one month following the second vaccination:**

289 The proportion of participants with hSBA ≥1:5, one month following the second dose

290 of 4CMenB vaccine, were generally similar for reference strains 44/76-SL and 5/99

291 in both vaccine lots (99% each and 100% each, respectively). For the NZ98/254

292 strain, a higher proportion of participants in Lot 2 (79%, CI 72-86) presented with

293 hSBA ≥1:5 compared to Lot 1, 70% (62-77) In addition (although statistically

294 equivalent), the ELISA GMR to baseline against NHBA antigen was slightly higher

295 in Lot 2 (153 (CI 131-179) compared to Lot 1 (122 (103-143). Reverse cumulative

296 distribution (RCD) functions of hSBA titres were similar for the two groups (Lot 1

297 and 2) for each of the 3 reference strains 44/76-SL, 5/99 and NZ98/254 and for

298 ELISA concentrations for NHBA antigen, both at baseline and at one month

299 following the second vaccination.

300

301 **Immune response at two weeks following the second vaccination:**

302 In the subset population, two weeks and one month following 4CMenB, 100% of

303 participants in both Lot 1 and Lot 2 groups attained hSBA ≥ 1:5 against reference

304 strains 44/76-SL and 5/99. However against strain NZ98/254, only 84% and 96% of

305 adolescents achieved an hSBA titre ≥ 5 at 2 weeks, and these proportions fell to 64%

306 and 80% by 1 month following the second vaccination, for Lot 1 and Lot 2,

307 respectively (Figure 2).

308

309 In general, for both Lot 1 and Lot 2 vaccines, there was a substantial but non-uniform

310 decline in hSBA GMT levels for the 3 reference strains and ELISA GMCs against the

311 NHBA antigen, from two weeks to one month following the second vaccination

312 (Table 2). RCD curves of the hSBA titres and ELISA concentrations at two weeks

313 and at one month after second vaccination are shown in Figure 1. For both lots, and

314 for hSBA titres against each reference strain and ELISA concentrations against

315 NHBA antigen, separation (shift to the left) is noted between the RCD at two weeks

316 and one month following the second vaccination, indicating a decline in immune

317 response between these 2 time-points.

318 No meaningful differences were observed in the pattern of the immune responses at

319 any time point, when analyzed by center and country

320

321 **Safety and Tolerability**

322 Overall, both lots of 4CMenB had similar safety profiles and were generally well

323 tolerated. Almost all adolescents (98% in Lot 1 and 99% in Lot 2) reported at least

324 one local, systemic or other reaction during the 7 days after either vaccination. The

325 proportion of participants with local reactions was similar between groups (96% Lot 1

326 and 98% Lot 2). Most local and systemic reactions were mild to moderate in nature

327 (Tables 3 and 4). The most frequently reported local reaction after any vaccination

328 was pain (96% and 98%), reported as severe in 14% and 17% of Lot 1 and 2

329 participants, respectively. The most frequently reported solicited systemic reaction

330 was myalgia (59% and 68%), followed by headache (44% and 51%) and fatigue (44%

331 and 49%) in Lot 1 and 2 participants, respectively. Fever $\geq 38°C$ was infrequently

332 reported (5% and 3% in Lot 1 and 2 participants respectively). One participant in Lot

333 2 withdrew from the study on day 34 due to an adverse event (infectious

334 mononucleosis) that started in day 14, with moderate severity and was judged as

335 unrelated to the study vaccine by the investigator. No death, serious adverse event or

336 pregnancy occurred.

337

Discussion

We evaluated the consistency and kinetics of the immune response following

vaccination with one of two lots of 4CMenB administered as two doses, one month

apart in healthy 11-17 year old adolescents. We found immunological equivalence

between two lots of 4CMenB at one month after second vaccination in terms of hSBA

GMTs against each of the three MenB reference strains for fHbp, NadA and PorA

antigens and ELISA IgG GMCs against the NHBA antigen. A variable but a

substantial decline in GMTs/GMCs was observed from two weeks to one month

following the second vaccination. However it should be noted that protective titers

(hSBA ≥5) were maintained in 100% of subjects for strains 44/76-SL and 5/99 and in

75% subjects for strain NZ98/254, even at one month. Low levels of pre-existing

immunogenicity to the meningococcal vaccine antigens, suggest the possibility of

little environmental exposure to these meningococcal reference strains in the

Australian and Canadian adolescent population.

This is the first study to measure the early immune response following 4CMenB

vaccination. It was postulated that immune responses may remain static or decline

slightly from 2 to 4 weeks following 4CMenB vaccination in adolescents. However, a

substantial decline over the two weeks was not expected. The finding of the peak

antibody response at 14 days following immunization is similar to that reported

following meningococcal serogroup C conjugate vaccine, *Haemophilus influenzae*

type b (Hib) polysaccharide and Hib conjugate vaccines (peak at 10-14 days), which

subsequently wane [19-21]. Recently, measurement of the longer term kinetics of

immune responses following the second dose of 4CMenB vaccine in university

362   students has shown ongoing waning of hSBA titers from 1-month to 11-months

363   following vaccination [22].

364

365   Also of note, we found a difference in the rate of decline of hSBA titres between the

366   strains from two weeks to one month following the second 4CMenB vaccination. The

367   largest declines (a fall in hSBA GMT of 48%) were observed for reference strains

368   5/99 and NZ98/254 against the NadA and PorA vaccine antigens respectively. The

369   PorA antigen also generated the lowest peak immune response of the four vaccine

370   components (as determined by fold-rise from baseline to two weeks following the

371   second vaccination and proportion of adolescents generating titres considered

372   protective, hSBA ≥5). Lower seroresponses to this same PorA antigen (NZ98/254)

373   have previously been reported. Following three doses of the monovalent MenB OMV

374   vaccine (MeNZB) used to help control a clonal outbreak in New Zealand: only 74%

375   of 6-8 month-old [23], 75% of 16-24 month-old [24] and 74-79% of 8-12 year-old

376   children [25] developed a seroresponse, as assessed at 4 weeks after dose 3 (four-fold

377   rise in hSBA titre compared to baseline). Age-dependent antibody decline against this

378   PorA vaccine antigen was also described; 7 months following the third dose of

379   MeNZB in 6-8 month-old infants only 28% had persistent hSBA ≥4; compared to

380   36%, 14 months following the third dose in 8-12 year-old children; and 50%, 10

381   months following the third dose in adults [26]. Accordingly, as the rate of decline of

382   hSBA titres (or waning of antibody) is differential according to age and strain, it is

383   possible that susceptibility to meningococcal infection and duration of vaccine

384   protection might be differential according to age and geographical region (depending

385   on the expression of proteins in the circulating disease-causing strains). Importantly,

386   vaccine efficacy has been shown to mirror a rapid decline in circulating bactericidal

387   antibodies following vaccination with monovalent MenB OMV vaccines in Norway

388   and New Zealand [27, 28] and with MenC conjugate vaccines in the UK [29].

389

390   This study highlights the complexity in assessing immunogenicity and determining

391   generalizability of the four-component MenB vaccine for different geographical

392   regions. At baseline, pre-existing immunity to the meningococcal vaccine antigens in

393   our Australian and Canadian adolescent population was low (2%–7%) of adolescents

394   had hSBA titres ≥5 to strains for fHbp, NadA and PorA antigens, respectively,

395   compared to 34%–44% with hSBA titres ≥4 in a prior 4CMenB adolescent study

396   conducted in Santiago and Valparaiso, Chile [17]. In the current study, while 99-

397   100% of adolescents achieved protective titres (hSBA ≥5) to reference strains 44/76-

398   SL and 5/99, one month following the second 4CMenB vaccination, only 75% did so

399   for the NZ98/254 strain. In comparison, in the Chilean study, 99-100% of adolescents

400   achieved hSBA titres ≥ 4 (albeit a slightly less conservative measure) to each of these

401   3 reference strains [17]. The difference in baseline immunogenicity between the two

402   similar 11-17 year-old adolescent vaccine-naïve populations could partially relate to

403   assays conducted in to different laboratories, but may more likely be due to different

404   levels of acquisition of natural immunity though nasopharyngeal carriage in each

405   population. Higher baseline immunogenicity levels may suggest higher levels of

406   environmental exposure to the meningococcal vaccine strains in Chilean than in the

407   Canadian and Australian populations. Indeed, even accounting for different

408   laboratories, the RCD function curves of hSBA responses for the reference strain

409   NZ98/254 (PorA) in Chilean adolescents, who received the accelerated two-dose

410   schedule (one month apart), were noticeably shifted to the right (higher hSBA titres)

411   compared to the current study. However hSBA titres were similar against reference

412   strains 44/76-SL and 5/99 in both studies [17]. Further, Chilean adolescents with

413   higher baseline levels (hSBA titres ≥4) generated higher post vaccination antibody

414   titres than vaccine antigen naïve adolescents (hSBA titres <4 at baseline) and these

415   differences persisted up to 6 months [17]. Recently, assays done in a subset of

416   University students in a UK meningococcal carriage study found high baseline

417   immunity to the 4CMenB vaccine antigens, similar to the Chilean study (these assays

418   were also performed at Public Health England laboratory, UK) [22] together with

419   high rates of carriage (33%) [30]. In comparison, meningococcal carriage rates are

420   low in Canada. No carriage data are available for Australia. Accordingly, in

421   populations with low baseline immunity to MenB, persistence of antibody may be

422   reduced. The possibility of an additional vaccine impact on carriage may further

423   amplify these differences in population-specific effects.

424

425   The hSBA GMTs and ELISA GMCs at one month after second vaccination in the two

426   vaccine groups were statistically equivalent for each of the three MenB reference

427   strains for vaccine antigens fHbp, NadA PorA and NHBA antigen, respectively. This

428   finding was not unexpected. Both vaccine lots were identical in composition, but

429   formulated with OMV manufactured at two different facilities.

430

431   There was a slightly higher frequency of systemic reactions reported by adolescents

432   who received Lot 2 vaccine (compared to Lot 1). Overall, the rate of reported

433   systemic reactions was slightly higher in our study than previously reported, although

434   rates of fever ≥ 38°C were similar [17]. Of note, in both studies the vast majority of

435   reported systemic reactions were of mild or moderate severity, a similar number were

436 reported as severe and no evidence of increasing rates of reactions with subsequent

437 dosing was identified [17].

438

439 The 4CMenB (Bexsero®) vaccine was licensed for use in the European Union in

440 January 2013, and subsequently in Australia, Canada and some Latin American

441 countries, for individuals from 2 months-of age [31]. In March 2014, the UK became

442 the first country to recommend its use in a National Immunization Program (at 2, 4

443 and 12 months of age) [32] where coverage of 4CMenB is estimated at 88% of

444 invasive MenB strains [33] (subject to vaccine pricing and cost-effectiveness

445 requirements by the UK Government). In addition, a second MenB vaccine, a bivalent

446 vaccine containing recombinant factor H binding protein variants (also called

447 rLP2086), manufactured by Pfizer, has undergone Phase II clinical trials [34-36] and

448 was licensed in the US in October 2014 for use in adolescents and young adults. Both

449 4CMenB and rLP2086 had received Breakthrough Therapy designation from the US

450 FDA. In January 2015, 4CMenB was also approved in United States (US) as a 2-dose

451 series in adolescents 11- 25 years ( ) .

452

453 In conclusion, this study demonstrated the lot to lot consistency of 4CMenB vaccine

454 manufactured at different sites. Two doses of 4CMenB, given one month apart, had

455 an acceptable safety profile and induced robust immune responses in adolescents,

456 though waning of titers was observed from 2 weeks to 1 month after vaccination.

457 Further, this study's finding of differential baseline antibody titres to 4CMenB

458 vaccine antigens compared with age-matched but geographically distinct populations,

459 affecting immunogenicity, is important. Population-based post-implementation

460   disease surveillance to assess the potential differential vaccine impact (on herd

461   immunity and duration of protection) in each region will be imperative.

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