Sponsor:	Chiron S.r.l.
Investigational Product:	Combined Meningococcal (group C) oligosaccharide diphtheria CRM-197 - *Haemophilus influenzae* type b (MenC-Hib) conjugate vaccine
Indication:	Prophylaxis against *Haemophilus influenzae* type b (Hib)
Protocol Number:	V82P1
Protocol Title:	A Phase I/II, Single Center, Partially Observer-Blind, Controlled, Randomized Study to Explore Safety and Immunogenicity in Healthy Adult Subjects who Receive Either One Dose of Chiron Combined MenC-Hib Conjugate Vaccine, OR Separate Administration of Chiron Hib Conjugate Vaccine (VaxemHib®) and Chiron MenC Conjugate Vaccine (Menjugate®), OR One Dose of Menjugate®, OR One Dose of VaxemHib®
Phase of Development:	Phase I/II
Study Period:	
Date of first enrolment:	06 SEP 04
Date of last visit:	10 NOV 04

Methodology:

This was a Phase I/II, single center, randomized, controlled, partially observer-blind study to be performed over a period of approximately 7 weeks. Overall, 106 healthy adults aged 18 to 50 years were randomized in a 2:1:1:1 ratio to receive either one dose of combined MenC-Hib conjugate vaccine (Group A, called Mixed in the Results tables), or separate but concomitant administrations of VaxemHib and Menjugate (Group B, called Separate in the Results tables), or one dose of Menjugate (Group C, called Men C in the Results tables), or one dose of VaxemHib (Group D, called Hib in the Results tables).

Vaccines were administered intramuscularly (IM) in the deltoid muscle (MenC-Hib vaccine in the right arm and VaxemHib and Menjugate vaccines in the right and in the left arm, respectively). Subjects were observed for 30 minutes after vaccination for any immediate reactions and were also instructed to complete a diary card for both local (i.e., pain, erythema and induration) and systemic reactions (i.e., malaise, chills, headache, nausea, myalgia and arthralgia) for 7 days (i.e. Day 1 to Day 7) following vaccination. During this period the axillary temperature were recorded daily, possibly at the same time of the day. The use of analgesic/antipyretic medication were collected during the same period. Subjects were contacted by phone at 8 days after vaccination to obtain local and systemic reaction data and to determine their clinical status. The diary cards were

collected during the following site visit. All adverse events, including all serious adverse events and/or adverse events necessitating a physician's visit and/or resulting in premature subject's withdrawal from the study were collected throughout the study and recorded by study personnel during the second study visit. All prescription medication, including non-study vaccines, except minerals and vitamins, taken at any time during the trial were recorded. All non-prescription medication were recorded for seven days following vaccination.

During the study, all reported adverse events were followed until resolution or diagnosis. If an adverse event remained unresolved at the conclusion of the study, a clinical assessment were made by the Investigator and the Chiron medical monitor whether continued follow-up of the adverse event was warranted.

Serum samples for immunogenicity assays were collected before vaccination (visit 1, Day 1) and on Day 29 (visit 2, window: 29-36).

Number of Subjects (planned and analyzed):

A total of 100 adult subjects aged 18 to 50 years were planned to be enrolled. A total of 106 subjects were screened, and all of them were enrolled and analyzed.

Study Centers:

1 center in Italy.

Publication (reference) and/or ClinicalTrials.gov National Clinical Trial (NCT) Number:

None.

Objectives:

Safety Objectives

To explore the safety and tolerability in healthy adult subjects aged 18-50 years who receive either one dose of Chiron combined MenC-Hib conjugate vaccine, or separate administration of Chiron Hib conjugate vaccine (VaxemHib®) and Chiron MenC conjugate vaccine (Menjugate®), or one dose of Menjugate® or one dose of VaxemHib®.

Immunogenicity Objectives

• To explore the serum anti-PRP antibody response, as measured by ELISA, and the serum antibody response to *N. Meningitidis* serogroup C, as measured by rabbit complement Bactericidal Assay (rSBA) Geometric Mean Titer (GMT), at one month after the administration of Chiron combined MenC-Hib conjugate vaccine and of the separate

administration of Chiron Hib conjugate vaccine (VaxemHib®) and Chiron MenC conjugate vaccine (Menjugate®) in healthy adult subjects aged 18-50 years.

• To measure the serum antibody response to N. *Meningitidis* serogroup C, as measured by rSBA GMT, at one month after the administration of Menjugate® in healthy adult subjects aged 18-50 years. To measure the serum anti-PRP geometric mean antibody response, as measured by ELISA, at one month after the administration of VaxemHib® in healthy adult subjects aged 18-50 years.

Test Product, Dose, Mode of Administration, Lot Number:

The combined MenC-Hib conjugate vaccine contained active substances (Hib-CRM and MenC-CRM) and adjuvant (aluminum phosphate). The lot number: UA2210A.

A single 0.5 mL dose was administered IM in the deltoid muscle of the left arm.

VaxemHib contained active substance Hib oligosaccharide and diptheria toxoid (CRM-197). The lot number for VaxemHib Hib-CRM197: T32P30H1.

A single 0.5 mL dose was administered IM in the deltoid muscle of the right arm.

Duration of Study:

A total of 7 week: three weeks for enrollment and 4 weeks of subject's participation.

Reference Therapy, Dose, Mode of Administration, Lot Number:

A single dose of each of the reference vaccines (VaxemHib and Menjugate), each supplied as 0.5 mL volumes, was administered by the IM route in the deltoid muscle of the right and left arm, respectively.

Menjugate vaccine contained active substances Meningococcal C oligosaccharide and Diptheria toxoid (CRM 197).

The lot numbers of the vaccines are:

- VaxemHib Hib-CRM197 - Lot: T32P30H2
- MenC vaccine - MenC-CRM197 Lot: UA2210A.

Statistical Methods:

This was an exploratory trial and was not intended to test superiority or equivalence between vaccines. As this was an exploratory trial there was no statistical (null) hypothesis associated with the primary safety objective. All analyses were run descriptively.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion criteria: Individuals eligible for enrollment into this study were male and female adult volunteers who were 18 to < 51 years, mentally competent, willing and able to give written informed consent prior to study entry, able to comply with all the study requirements, in general good health (determined by medical history, physical examination, clinical judgment of the investigator).
Exclusion criteria: Subjects were not to be enrolled into the study if they had any serious disease; they had a history of any anaplylactic shock, pulmonary reactivity or any allergic reaction after previous vaccinations; they had a known or suspected impairment of immune function; they had previously received any conjugate Meningococcal C vaccine; they had received any diphtheria vaccine or any vaccine containing a diphtheria component within the past 5 years; they had received any other vaccine or any investigational agent within the past 4 weeks; they had household contact with and/or intimate exposure to an individual with culture proven *N. Meningitidis* serogroup C or *H. influenzae* type b infection, within the previous 60 days.

Criteria for Evaluation:

Safety

Number and percentages of subjects who reported:

- local reactions (pain, erythema and induration) within 7 days after vaccination
- systemic reactions (malaise, chills, headache, nausea, myalgia and arthralgia) within 7 days after vacciantion
- serious adverse events and/or adverse events necessitating a physician's visit and/or resulting in premature withdrawal from the study, per vaccination group between day 1 and the study termination visit (day 29-36).

Immunogenicity

- Anti-PRP antibody titer by ELISA at one month after vaccination of subjects belonging to Groups A, B and D.
- Anti-N. *Meningitidis* serogroup C antibody titer by rabbit complement bactericidal assay (rSBA) at one month after vaccination of subjects belonging to Groups A, B and C.

Results:

Table 1: Overview of Subject Populations

	Mixed	Separate	MenC	Hib	TOTAL
	N = 42	N = 21	N = 21	N = 22	N = 106
Population:					
Enrolled	42 (100%)	21 (100%)	21 (100%)	22 (100%)	106 (100%)
Immunogenicity - PP	40 (95%)	19 (90%)	20 (95%)	21 (95%)	100 (94%)
Safety	42 (100%)	21 (100%)	21 (100%)	22 (100%)	106 (100%)

Abbreviations. PP – Per Protocol Population.

Table 2: Summary of Study Terminations - All Enrolled Subjects

	Mixed	Separate	MenC	Hib	TOTAL
Enrolled	42	21	21	22	106
Completed protocol	42 (100%)	21 (100%)	21 (100%)	22 (100%)	106 (100%)

Table 3: Demographic and Other Baseline Characteristics - All Enrolled Subjects

	Mixed	Separate	MenC	Hib
	N = 42	N = 21	N = 21	N = 22
Age (Years):	35.0±8.3	38.3±7.5	38.8±7.9	37.5±9.4
Sex				
Male	8 (19%)	5 (24%)	6 (29%)	8 (36%)
Female	34 (81%)	16 (76%)	15 (71%)	14 (64%)
Race				
Caucasian	42 (100%)	21 (100%)	21 (100%)	21 (95%)
Black	0	0	0	1 (5%)
Weight (kg)	65.73±16.20	68.66±11.92	71.17±14.77	69.55±11.32
Height (cm)	164.8±8.1	165.2±6.4	166.4±10.0	165.9±7.8

Categorical parameters: N (%), non-categorical parameters: mean±standard deviation.
N = number of subjects.

Table 4: Overview of Solicited Local Reactions – Safety Population

		Mixed N=42	Separate N=21	MenC N=21	Hib N=22
Any		17 (40%)	16 (76%)	14 (67%)	10 (45%)
Erythema	Any	2 (5%)	5 (24%)	2 (10%)	2 (9%)
Induration	Any	2 (5%)	5 (24%)	5 (24%)	3 (14%)
Pain	Any	14 (33%)	16 (76%)	12 (57%)	10 (45%)

N = number of subjects.

Table 5: Overview of Solicited Systemic Reactions – Safety Population

		Mixed N=42	Separate N=21	MenC N=21	Hib N=22
Any		17 (40%)	11 (52%)	9 (43%)	14 (64%)
Chills	Any	3 (7%)	1 (5%)	2 (10%)	4 (18%)
Malaise	Any	5 (12%)	3 (14%)	2 (10%)	6 (27%)
Myalgia	Any	7 (17%)	6 (29%)	2 (10%)	6 (27%)
Arthralgia	Any	4 (10%)	3 (14%)	3 (14%)	3 (14%)
Nausea	Any	2 (5%)	1 (5%)	1 (5%)	4 (18%)
Headache	Any	13 (31%)	7 (33%)	5 (24%)	7 (32%)
Fever (≥38°C)	Yes	0	2 (10%)	0	1 (5%)
Other					
Stayed home due to reaction	Yes	0	0	0	0
Analgesic/antipyretic medication used	Yes	4 (10%)	6 (29%)	3 (14%)	5 (23%)

Table 6: Overview of Unsolicited AEs – Safety Population

	Mixed N=42	Separate N=21	MenC N=21	Hib N=22
Any AEs	2 (5%)	0	0	1 (5%)
At least possibly related AEs	0	0	0	0
Serious AEs	0	0	0	0
AEs leading to discontinuation	0	0	0	0
Death	0	0	0	0

Table 7: Anti-PRP antibody titer by ELISA at one month after vaccination of subjects belonging to Groups A, B and D

	Geometric Mean Titers (95% CI)		
	Mixed N=41	**Separate N=21**	**Hib N=22**
Baseline	0.98 (0.61 – 1.57)	0.87 (0.45 – 1.68)	1.45 (0.76 – 2.76)
1 month after vaccination	61 (36 – 103)	52 (25 – 107)	41 (20 – 84)

Abbreviation: PRP=Polyribosyl Ribitol Phosphate, CI= confidence interval.

Table 8: Anti-*N. Meningitidis* serogroup C antibody titer by rabbit complement bactericidal assay (rSBA) at one month after vaccination of subjects belonging to Groups A, B and C

	Geometric Mean Titers (95% CI)		
	Mixed N=40	**Separate N=19**	**MenC N=20**
Baseline	6.73 (4.1 – 11)	3.33 (1.62 – 6.84)	3.36 (1.67 – 6.78)
1 month after vaccination	1448 (637 – 3295)	178 (54 – 586)	699 (219 – 2237)

Abbreviation: CI, confidence interval.

Table 9: Serious Adverse Events by Preferred Term Sorted by System Organ Class – Safety Population

None reported.

Table 10: Unsolicited AEs Reported by > 5% of Subjects by Preferred Term Sorted by System Organ Class – Safety Population

None reported.

Conclusion:

- The percentage of subjects reporting any local and systemic reactogenicity were lowest in the Mixed arm and highest in the Separate and Hib administration arms for local and systemic adverse reactions, respectively.
- The anti-PRP antibody titers one month after vaccination were acceptable and similar for Mixed, Separate and Hib arms, respectively 61 (95%CI: 36-103), 52 (95%CI: 25-107) and 41 (95%CI: 20-84).
- The anti-N meningitidis serogroup C antibody titers by rabbit complement were very robust for Mixed, Separate and MenC arms; respectively 1448 (95%CI: 637-3295), 178 (95%CI: 54-586) and 699 (95%CI: 219-2237). Based on non-overlapping titers, titers were higher in the Mixed arm than in the Separate arm.

Date of Clinical Trial Report: Not available.