2 Synopsis

Sanofi Pasteur MSD **CLINICAL STUDY REPORT**

SYNOPSIS

PR5I, suspension for injection, active immunisation against Diphtheria, Tetanus, Pertussis, Poliomyelitis (caused by poliovirus types 1, 2, and 3), infection caused by Hepatitis B virus, and against invasive disease caused by *Haemophilus influenzae* type b

PROTOCOL TITLE/NO.:

A phase III open-label randomised study, to evaluate the immunogenicity and safety of the concomitant administration of V419 (PR5I) given at 2, 3, and 4 months of age with two types of meningococcal serogroup C conjugate (MCC) vaccines given at 3 and 4 months of age, and followed by the administration at 12 months of age of a combined *Haemophilus influenzae* type b-MCC vaccine.

Study Identification Number: PRI01C
EudraCT Number: 2011-002413-11

INVESTIGATOR/STUDY CENTRES:

Coordinating investigator: PPD United Kingdom (UK).

This study was conducted at 11 centres in the UK.

PRIMARY THERAPY PERIOD:	**CLINICAL PHASE:**
30-MAR-2012 (First Patient Entered) to 27-SEP-2013 (Last Patient Last Visit)	III

DURATION OF VACCINATION:

The vaccination period lasted 10 months and was split in 2 parts:

- **Part I referred to the infant doses**

  Subjects received the first dose of PR5I at 2 months of age. One (1) and 2 months later (at 3 and 4 months of age), they concomitantly received 1 dose of PR5I and 1 dose of meningococcal serogroup C conjugate (MCC) vaccine either conjugated with tetanus toxoid (MCC-TT vaccine) or CRM197 (MCC-CRM vaccine).

- **Part II referred to the booster/toddler dose**

  Subjects received 1 dose of a combined *Haemophilus influenzae* type b (Hib)-MCC vaccine at 12 months of age, i.e. 10 months after the first dose of PR5I.

Routine vaccines were given in Part I and Part II: 13-valent pneumococcal conjugate vaccine (PCV-13) at 2, 4, and 12 months of age and measles, mumps, and rubella (MMR) vaccine at 12 months of age.

OBJECTIVES:

Primary Objective

IMMUNOGENICITY

Part **I**

- To evaluate the concomitant administration of PR5I with 2 types of MCC vaccines (MCC-TT and MCC-CRM) to healthy infants at 3 and 4 months of age in terms of seroprotection rate (SPR) to MCC.

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OBJECTIVES (*Cont.*):

Secondary Objectives

IMMUNOGENICITY

Part **I**

- To evaluate the immunogenicity of PR5I in terms of SPR to Hib when PR5I was given at 2 months of age and concomitantly with MCC vaccines at 3 and 4 months of age
- To describe the immunogenicity of PR5I when PR5I was given at 2 months of age and concomitantly with MCC vaccines at 3 and 4 months of age
- To describe the immunogenicity of MCC vaccines when MCC vaccines were given concomitantly with PR5I at 3 and 4 months of age (post-dose 1 and post-dose 2).

Part **II**

- To describe the immunogenicity of Hib-MCC vaccine given at 12 months of age in subjects who received PR5I at 2, 3, and 4 months of age.

SAFETY

Part **I**

- To describe the safety of PR5I given concomitantly with PCV-13 at 2 months of age, concomitantly with MCC vaccines at 3 months of age, and concomitantly with both PCV-13 and MCC vaccines at 4 months of age.

Part **II**

- To describe the safety of Hib-MCC vaccine given concomitantly with PCV-13 and MMR vaccine at 12 months of age in subjects who received PR5I at 2, 3, and 4 months of age.

HYPOTHESES:

Primary Hypotheses

IMMUNOGENICITY

Part **I**

- The first primary hypothesis was that the SPR to MCC as measured 1 month post-dose 2 of a MCC-TT vaccine was acceptable when administered concomitantly with PR5I
- The second primary hypothesis was that the SPR to MCC as measured 1 month post-dose 2 of a MCC-CRM vaccine was acceptable when administered concomitantly with PR5I.

The SPR to MCC was defined as the proportion of subjects with an anti-MCC titre ≥1:8 dilution (dil).

The SPR to MCC was considered as acceptable if the lower bound of its 2-sided 95% confidence interval (CI) (adjusted for multiplicity) was >90%. Success of the study required that the primary objective was achieved for at least 1 type of MCC vaccine (MCC-TT or MCC-CRM vaccine): i.e. at least 1 of the 2 primary null hypotheses was rejected. To control the overall Type I error at the 2-sided alpha of 0.05 (1-sided alpha of 0.025), the Hochberg adjustment step-up procedure [1] was used to determine the overall study success.

[1] Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988; 75 (4): 800-2

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HYPOTHESES (*Cont.*):

Secondary Hypotheses

IMMUNOGENICITY

Part **I**

- The secondary hypothesis was that the SPR to Hib as measured 1 month post-dose 3 of PR5I was acceptable when administered concomitantly with MCC vaccines.

SPR to Hib-polyribosylribitol phosphate (PRP) was defined as the proportion of subjects with an anti-PRP titre ≥0.15 micrograms (µg)/millilitres (mL). The SPR to Hib was considered as acceptable if the lower bound of its 2-sided 95% CI was >80%.

Part **II**

- No formal hypothesis was tested.

SAFETY

Part **I and** Part **II**

- No formal hypothesis was tested.

STUDY DESIGN:

This was a randomised, open-label, multicentre study evaluating 2 MCC vaccines when given concomitantly with PR5I.

A total of 284 (142 subjects per MCC vaccine group) healthy 2-month-old infants were to be randomised with a ratio 1:1 to receive MCC-TT vaccine (MCC-TT group or Group 1) or MCC-CRM vaccine (MCC-CRM group or Group 2).

Each included subject was to attend 6 visits:

- **Part I (infant doses):** Visit 1 at 2 months of age (46 to 74 days of age), Visit 2 at 3 months of age (28 to 44 days after Visit 1), Visit 3 at 4 months of age (28 to 44 days after Visit 2), and Visit 4 at 5 months of age (28 to 44 days after Visit 3)
- **Part II (booster/toddler dose):** Visit 5 at 12 months of age (365 to 403 days of age), and Visit 6 at 13 months of age (28 to 44 days after Visit 5).

Vaccinations were to be performed at Visits 1, 2, 3, and 5.

Blood specimens were to be collected at Visits 1 (blood sample [BS]1), 3 (BS2), 4 (BS3), 5 (BS4), and 6 (BS5). BS1 and BS4 were pre-vaccination samples to be collected on the visit day itself or within 5 days prior to the visit; BS2, BS3, and BS5 were post-vaccination samples to be collected 28 to 44 days after vaccination.

The recruitment period was scheduled to last about 6 months.

Each included subject was to be in the study for around 11 months.

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SUBJECT/PATIENT DISPOSITION:

Overall, 11 investigational sites were evaluated and considered eligible to screen subjects for study participation. These 11 sites included and randomised 284 subjects in total.

Part I: Of the 284 randomised subjects, 282 (99.3%) received the 3 doses of PR5I and the 2 doses of MCC vaccine and 281 (98.9%) completed Part I of the study. Two (2) subjects voluntarily withdrew from the study: 1 in the MCC-TT vaccine group before receiving the third vaccination series (PR5I dose 3, MCC-TT vaccine dose 2, and PCV13 dose 2) and 1 in the MCC-CRM group before receiving the second vaccination series (PR5I dose 2 and MCC-CRM vaccine dose 1). One (1) subject in the MCC-TT group completed study vaccination but was lost to follow-up between Visits 3 and 4.

Part II: Of the 281 subjects who completed Part I of the study, 276 (98.2%) entered Part II of the study. Reasons leading to study discontinuation between Part I and Part II were voluntary withdrawal (4 cases) and lost to follow-up (1 case). Of the 276 subjects who entered Part II of the study, 276 (100%) received the Hib-MCC vaccine dose. Of these, 266 (96.4%) completed Part II of the study. Reasons leading to study discontinuation were voluntary withdrawal (5 cases) and loss to follow-up (5 cases).

The disposition of subjects is provided by MCC vaccine groups for Part I (on Randomised Set) in Table S1 and for Part II (on Subjects who Completed Part I) in Table S2. The characteristics of subjects at inclusion (Part I) are provided by MCC vaccine groups (on Randomised Set) in Table S1.

Table S1: Subject Disposition and Subject Characteristics – Part I (Randomised Set)

	MCC-TT		MCC-CRM		Total	
Randomised subjects [1], n (%)	142	-	142	-	284	-
Vaccinated at:						
Visit 1, n (%)	142	(100)	142	(100)	284	(100)
Visit 2, n (%)	142	(100)	141	(99.3)	283	(99.6)
Visit 3, n (%)	141	(99.3)	141	(99.3)	282	(99.3)
Received all 3 doses of PR5I [1], n (%)	141	(99.3)	141	(99.3)	282	(99.3)
Received all 2 doses of MCC vaccine [1], n (%)	141	(99.3)	141	(99.3)	282	(99.3)
Completed the Part I of the study [1, 2], n (%)	140	(98.6)	141	(99.3)	281	(98.9)
Did not complete the Part I, n (%)	2	(1.4)	1	(0.7)	3	(1.1)
Gender Male, n (%)	80	(56.3)	75	(52.8)	155	(54.6)
Female, n (%)	62	(43.7)	67	(47.2)	129	(45.4)
Age (days) [3], mean (SD) [range]	62.6 (6.7)	[47 to 76]	61.6 (7.2)	[47 to 75]	62.1 (7.0)	[47 to 76]

n (%) = number and percentage of subjects; SD = standard deviation.
Subjects received PR5I at 2, 3, and 4 months, MCC-TT/MCC-CRM vaccine at 3 and 4 months, and PCV-13 at 2 and 4 months.
Percentages are based on the number of randomised subjects.
[1] Subjects are classified by the MCC vaccine assigned at randomisation.
[2] Subject completed the Part I of the study if the subject has not discontinued prior or on the date of Visit 4.
[3] Age is calculated as (date of vaccination dose 1 – date of birth) +1
Source: Listing 16.2.1.b, Listing 16.2.4.a, and Listing 16.2.5.a

SUBJECT/PATIENT DISPOSITION (*Cont.*):

Table S2: Subject Disposition – Part II (Subjects Who Completed Part I)

	MCC-TT		MCC-CRM		Total	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Completing Part I of the study [1]	140		141		281	
Discontinued between Part I and Part II [1,2]	3	(2.1)	2	(1.4)	5	(1.8)
Entering Part II of the study [1,2,4]	137	(97.9)	139	(98.6)	276	(98.2)
Received Hib-MCC vaccine [1,3]	137	(100)	139	(100)	276	(100)
Completed Part II of the study [1,3]	134	(97.8)	132	(95.0)	266	(96.4)
Did not complete the Part II [1,3]	3	(2.2)	7	(5.0)	10	(3.6)

n (%) = number and percentage of subjects.
Subjects received Hib-MCC vaccine, PCV-13, and MMR vaccine at 12 months.
[1] Subject completed the Part I of the study if the subject has not discontinued prior or on the date of Visit 4.
[2] Percentages are based on the number of subjects who completed Part I of the study.
[3] Percentages are based on the number of subjects who attended Visit 5 (entered in Part II of the study).
[4] Subjects who attended Visit 5.
Source: Listing 16.2.1.c

DOSAGE/FORMULATION NOS.:

The schedule of vaccination for each study group is provided in Table S3.

Table S3: Vaccine Administration by Vaccination Group

Group	Vaccine Administered		Visit 1 2 months	Visit 2 3 months	Visit 3 4 months	Visit 5 12 months
MCC-TT (n=141)	Test vaccines	PR5I	X	X	X	
		MCC-TT vaccine		X	X	
		Hib-MCC vaccine				X
	Routine vaccines	PCV-13	X		X	X
		MMR vaccine				X
MCC-CRM (n=143)	Test vaccines	PR5I	X	X	X	
		MCC-CRM vaccine		X	X	
		Hib-MCC vaccine				X
	Routine vaccines	PCV-13	X		X	X
		MMR vaccine				X

Each 0.5 mL dose of vaccine was injected via intramuscular (IM) route.
Test vaccines:
PR5I: diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus, *Haemophilus influenzae* b (Hib) conjugate [Meningococcal Outer Membrane Protein Complex], and hepatitis B (recombinant) vaccine.
MCC-TT vaccine: meningococcal group C polysaccharide conjugate vaccine to tetanus toxoid
MCC-CRM vaccine: meningococcal group C conjugate vaccine to CRM-197
Hib-MCC vaccine: *Haemophilus influenzae* type b and Meningococcal group C conjugate vaccine
Routine vaccines:
PCV-13: pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)
MMR vaccine: measles, mumps and rubella vaccine

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DOSAGE/FORMULATION NOS. (*Cont.*):

All administrations were to be done via intramuscular (IM) route. At 4 months of age (Visit 3), PCV-13 and MCC-TT/MCC-CRM vaccine injections were performed in the same thigh but separated by at least 5 centimetres (cm). At 12 months of age (Visit 5), PCV-13 and MMR vaccine injections were performed in the same thigh separated by at least 5 cm.

PR5I, MCC-TT/MCC-CRM vaccine, and PVC-13 were supplied in vials or pre-filled syringes containing 0.5 mL of sterile suspension for IM injection. Hib-MCC and MMR vaccines were supplied as a lyophilised powder for reconstitution with solvent for suspension for injection.

Vaccine component batch numbers are provided in Table S4.

Table S4: Vaccine Component Batch Numbers

Product Name	Short name	Batch Number (Bulk)
PR5I (Sanofi Pasteur Limited)	DTaP-HB-IPV-Hib	C3146B
NeisVac-C® (Baxter AG)	MCC-TT vaccine	VNS1L05A
Menjugate® (Novartis Vaccine and Diagnostics)	MCC-CRM vaccine	382011 and BA4559A
Menitorix® (GlaxoSmithKline)	Hib-MCC vaccine	A76CA209A
Prevenar 13® (Wyeth Lederle Vaccines)	PCV-13	F54378 and G29716
M-M-RVAXPRO® (Merck & Co. Inc.)	MMR vaccine	H010594 and H010453

Test vaccines:
PR5I: diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus, *Haemophilus influenzae* b (Hib) conjugate [Meningococcal Outer Membrane Protein Complex], and hepatitis B (recombinant) vaccine.
MCC-TT vaccine: meningococcal group C polysaccharide conjugate vaccine to tetanus toxoid
MCC-CRM vaccine: meningococcal group C conjugate vaccine to CRM-197
Hib-MCC vaccine: *Haemophilus influenzae* type b and Meningococcal group C conjugate vaccine

Routine vaccines:
PCV-13: pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)
MMR vaccine: measles, mumps and rubella vaccine

INCLUSION CRITERIA:

Healthy infants aged 46 to 74 days (both inclusive) on the day of PR5I dose 1 (Visit 1) with an informed consent signed by a parent/legal representative were included in this study if the parent/legal representative was able to comply with the study procedures such as adherence to study visits and completion of the vaccination report cards (VRCs).

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EVALUATION CRITERIA:

Immunogenicity Endpoints

PRIMARY ANALYSIS

Part I (only)

- Proportion of subjects with a post-dose 2 of MCC vaccine anti-MCC titre ≥1:8 dil.

SECONDARY ANALYSES

Part I

- Post-dose 1 of MCC vaccines
  - Proportion of subjects with an anti-MCC titre ≥1:8 dil
- Post-dose 1 and post-dose 2 of MCC vaccines
  - Proportion of subjects with an anti-MCC titre ≥1:128 dil
  - Anti-MCC geometric titres (GMTs) (dil)
- Post-dose 3 of PR5I
  - Proportion of subjects with an anti-PRP titre ≥0.15 µg/mL, anti-HBs titre ≥10 milli-international unit (mIU)/mL, anti-diphtheria titre ≥0.01 international unit (IU)/mL, and ≥0.1 IU/mL, anti-tetanus ≥0.01 IU/mL, and ≥0.1 IU/mL, anti-inactivated poliovirus (IPV) types 1, 2, and 3 titre ≥1:8 dil
  - Proportion of subjects with a seroresponse to pertussis toxoid (PT), filamentous haemagglutinin (FHA), pertactin (PRN), and fimbriae types 2 & 3 (FIM).
  - GMTs for all PR5I antigens: PRP (µg/mL), hepatitis B surface antigens (HBsAg) (mIU/mL), diphtheria (IU/mL), tetanus (IU/mL), poliovirus types 1, 2, and 3 (dil), PT, FHA, PRN, and FIM (enzyme-linked immunosorbent assay unit [EU]/mL).

  Pertussis seroresponse was defined as: (1) if the pre-vaccination antibody concentration was < lower limit of quantification (LLOQ), then the post-vaccination antibody concentration was to be ≥ LLOQ; (2) if the prevaccination antibody concentration was ≥ LLOQ, then the post-vaccination antibody concentration was to be ≥ pre-immunisation levels.

Part **II**

- Pre- and post-dose of Hib-MCC vaccine
  - Proportion of subjects with an anti-MCC titre ≥1:8 dil and ≥1:128 dil
  - Anti-MCC GMTs (dil)
  - Proportion of subjects with an anti-PRP titre ≥0.15 µg/mL and ≥1.0 µg/mL
  - Anti-PRP GMTs (µg/mL).

Due to evolution of practices, the term '*geometric mean titre (GMT)*', which was favoured at the time that the study protocol was written, has generally been replaced with '*geometric mean concentration (GMC)*', to refer to antibody concentrations measured in units. As '*titre*' may be defined as the concentration of a substance in solution, for simplicity in this document, serology results are reported as GMT and should be considered equivalent to GMC. Neither the serology assays nor the calculations have changed.

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EVALUATION CRITERIA (*Cont.*):

Safety Endpoints

Part I

The safety endpoints included proportions of subjects with solicited injection site (pain, erythema, swelling) and solicited systemic (pyrexia, vomiting, crying, somnolence, decreased appetite, irritability) adverse events (AEs) occurring from Day 1 to Day 5 after each vaccination, and unsolicited AEs (i.e. spontaneously reported injection site or systemic AE) reported from Day 1 through Day 15 after each vaccination. All injection site AEs were considered as vaccine-related and thus as injection site reactions.

Part I and Part II

Percentages of subjects with any serious adverse events (SAEs) from Day 1 to Day 15 after any vaccination were provided for each group and combined. Percentages of subjects with SAEs leading to death and with vaccine-related SAEs that occurred throughout the study were provided for each group and combined.

STATISTICAL PLANNING AND ANALYSIS:

Immunogenicity

Main analyses were performed on Per Protocol Sets (Part I or Part II PPS) and supportive analyses on Full Analysis Sets (Part I or Part II FAS).

The analysis sets and statistical methods employed for the immunogenicity analyses of the primary and the key secondary endpoints are provided in Table S5.

Descriptive statistics were employed for other secondary endpoints.

Table S5: Summary of Key Immunogenicity Analyses Performed

Analysis/Endpoint	Type of Analysis	Method [1]	Population	
			Main Analysis	Supportive Analysis
Primary Immunogenicity Analyses				
Acceptability - SPR to MCC 1 month post-dose 2 of MCC-TT vaccine	2-sided 95%* CI for single group proportion	Exact method for binary variables	Part I PPS	Part I FAS
Acceptability - SPR to MCC 1 month post-dose 2 of MCC-CRM vaccine	2-sided 95%* CI for single group proportion	Exact method for binary variables	Part I PPS	Part I FAS
Secondary Immunogenicity Analyses				
Acceptability - SPR to Hib 1 month post-dose 3 of PR5I	2-sided 95% CI for single group proportion	Exact method for binary variables	Part I PPS	Part I FAS

CI = confidence interval; FAS = Full Analysis Set; MCC = meningococcal group C; PPS = Per Protocol Set; SPR = seroprotection rate

* with appropriate multiplicity adjustment (Hochberg adjustment step-up procedure [2])

Part I PPS was defined as all randomised subjects excluding subjects with protocol violation which may interfere with the immunogenicity evaluation. Subjects were analysed according to the group to which they were randomised and vaccinated (i.e. deviation from the vaccination schedule allocated by randomisation led to exclusion from the PPS).

Part I FAS was defined as all randomised subjects who received at least one study vaccine during the Part I and have any post-vaccination immunogenicity evaluation associated with blood sample collected during the Part I of the study. Subjects were analysed according to the group to which they were randomised.

[1] Collet D. Modelling binary data; 2nd edition 2003, Chapman & Hall / CRC.
[2] Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988; 75(4): 800-2

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STATISTICAL PLANNING AND ANALYSIS *(Cont.)*:

Safety

Two (2) Safety Sets were defined for this study: **Part I Safety Set** was defined as all subjects who received at least 1 study vaccine during Part I and who have any safety follow-up data in Part I, and **Part II Safety Set** was defined as all subjects who received at least 1 study vaccine during Part II and who have any safety follow-up data in Part II.

Subjects were analysed according to the MCC vaccine they actually received in Part I as follows.

- **Part I:** Overall summary of AEs was provided after any vaccination performed for each group and combined
- **Part II:** Overall summary of all SAEs occurring from Day 1 to Day 15 was provided after vaccination at Visit 5 for each group and combined
- **Part I and Part II**: Overall summary of all SAEs leading to death or vaccine-related SAEs occurring from the signed informed consent to the last visit were provided for each group and combined.

RESULTS:

Immunogenicity Results

PRIMARY IMMUNOGENICITY ANALYSES

The analysis of acceptability of the **SPR to MCC** (i.e. proportion of subjects with an anti-MCC titre ≥1:8 dil) 1 month after 2 doses of MCC-TT or MCC-CRM vaccine based on the Part I PPS is provided in Table S6.

In both vaccine groups, the lower bound of the 2-sided 95% CI (with appropriate adjustment for multiplicity) of the SPR to MCC 1 month after 2 doses of MCC vaccine was greater than 90% (i.e. the prespecified acceptability threshold), demonstrating that the SPR for both MCC vaccines was acceptable.

Results based on the Part I FAS were comparable.

Table S6: Analysis of Acceptability of MCC Antigen Responses 1 Month Post-Dose 2 of MCC Vaccines When Given Concomitantly With PR5I (N=236) (Per Protocol Set - Part I)

Vaccine group	Endpoint	s/n	Alpha	Point estimate ([1-alpha]% CI) [1]	Lower bound limit	Conclusion: acceptability criterion met/not met
MCC-TT	% with titre ≥1:8 dil	121/121	0.050	100 [97.0, 100]	90%	Met
MCC-CRM	% with titre ≥1:8 dil	108/109	0.050	99.1 [95.0, 100]	90%	Met

CI = confidence interval, s/n = number of subjects with the response / number of subjects included in the analysis
[1] CI is calculated based on an exact binomial method by D. COLLETT.
Source: Listing 16.2.6.a

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RESULTS (*Cont.*):

SECONDARY IMMUNOGENICITY ANALYSES

Part I

- **Acceptability of PRP Seroprotection Rate 1 Month Post-dose 3 of PR5I**

The analysis of acceptability of the **SPR to Hib** (PRP) (i.e. proportion of subjects with an anti-PRP titre ≥0.15 µg/mL) 1 month after 3 doses of PR5I based on the Part I PPS is provided in Table S7.

The lower bound of the 2-sided 95% CI of the SPR to Hib (PRP) 1 month after 3 doses of PR5I was greater than 80% (i.e. the prespecified acceptability threshold), demonstrating that the SPR to Hib was acceptable for the combined vaccine groups.

Results based on the Part I FAS were comparable.

Table S7: Analysis of Acceptability of PRP Antigen Responses One Month Post-Dose 3 of PR5I (N=236) (Per Protocol Set - Part I)

Vaccine group	Endpoint	s/n	Point estimate (95% CI) [1]	Lower bound limit	Conclusion: acceptability criterion met/not met
Combined	% with titre ≥0.15 µg/mL	173/175	98.9 [95.9, 99.9]	80%	Met

CI = confidence interval, s/n = number of subjects with the response / number of subjects included in the analysis
[1] CI is calculated based on an exact binomial method by D. COLLETT.
Source: Listing 16.2.6.a

- **Descriptive Statistics for Post-Dose 1 and Post-Dose 2 Immunogenicity of MCC Vaccines Given at 3 and 4 Months of Age**

Descriptive statistics regarding MCC antigen responses 1 month post-dose 1 and post-dose 2 of MCC vaccines based on the Part I PPS are provided in Table S8.

The **SPRs and the proportions of subjects with an anti-MCC titre ≥1:128 dil** were comparable following 2 doses of MCC-TT vaccine (100% and 99.2%, respectively) or MCC-CRM vaccine (99.1% for both thresholds).

The **SPRs** were high and comparable after 1 dose of MCC-TT vaccine (100%) or MCC-CRM vaccine (96.4%); the **proportion of subjects with an anti-MCC titre ≥1:128 dil** was numerically higher after 1 dose of MCC-TT vaccine (98.0%) than after 1 dose of MCC-CRM vaccine (84.5%).

Based on non-overlapping CIs, the **GMTs** were higher after 1 or 2 doses of MCC-TT vaccine (1353.0 and 2024.7 dil, respectively) than after 1 or 2 doses of MCC-CRM vaccine (285.0 and 1077.4 dil, respectively).

Results based on the Part I FAS were comparable.

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RESULTS (*Cont.*):

Table S8: Summary of MCC Antigen Responses per Dose – Part I (N=236) (Per Protocol Set - Part I)

		MCC-TT (N=125)		MCC-CRM (N=111)		Total (N=236)	
Time point	**Endpoint**	**s/n**	**Observed response [95% CI] [1]**	**s/n**	**Observed response [95% CI] [1]**	**s/n**	**Observed response [95% CI] [1]**
Post-dose 1 of MCC vaccine	% with titres ≥1:8 dil	102/102	100 [96.4, 100]	81/84	96.4 [89.9, 99.3]	183/186	98.4 [95.4, 99.7]
	% with titres ≥1:128 dil	100/102	98.0 [93.1, 99.8]	71/84	84.5 [75.0, 91.5]	171/186	91.9 [87.0, 95.4]
	GMT		1353.0 [1058.4, 1729.6]		285.0 [201.5, 403.1]		669.6 [530.2, 845.6]
	n missing		23		27		50
Post-dose 2 of MCC vaccine	% with titres ≥1:8 dil	121/121	100 [97.0, 100]	108/109	99.1 [95.0, 100]	229/230	99.6 [97.6, 100]
	% with titres ≥1:128 dil	120/121	99.2 [95.5, 100]	108/109	99.1 [95.0, 100]	228/230	99.1 [96.9, 99.9]
	GMT		2024.7 [1689.8, 2425.9]		1077.4 [847.5, 1369.8]		1501.5 [1288.8, 1749.3]
	n missing		4		2		6

CI = confidence interval; n = number of subjects included in the analysis; s = number of subjects with the response
[1] The 95% CI for response rate is based on the exact binomial method by D. COLLETT. The 95% CI for GMT is based on the t-distribution of the natural log-transformed antibody titre.
Source: Listing 16.2.6.a

- **Descriptive Statistics for Post-Dose 3 Immunogenicity of PR5I Given at 2, 3 and 4 Months of Age**

Descriptive statistics regarding PR5I antigen responses 1 month after 3 doses of PR5I based on the Part I PPS are provided in Table S9.

For all PR5I antigens, results were comparable between the 2 vaccine groups.

On the combined analysis across vaccine groups, 1 month after a 3-dose primary series of PR5I given at 2, 3, and 4 months of age, the **SPR** against Hib (PRP) (i.e. proportion of subjects with a titre ≥0.15 µg/mL) and against HBsAg (i.e. proportion of subjects with a titre ≥10 mIU/mL) reached 98.9% and 96.6%, respectively. All the subjects were seroprotected against diphtheria (i.e. proportion of subjects with an anti-diphtheria titre ≥0.01 IU/mL), tetanus (i.e. proportion of subjects with an anti-tetanus titre ≥0.01 IU/mL and ≥0.1 IU/mL), and poliovirus types 1, 2 and 3 (i.e. proportion of subjects with an anti-poliovirus titre ≥1:8 dil). The **seroresponse rate** was ≥90.8% for all pertussis antigens.

Results based on the Part I FAS were comparable.

RESULTS (*Cont.*):

Table S9: Summary of PR5I Antigen Responses Post-Dose 3 of PR5I (N=236) (Per Protocol Set – Part I)

		MCC-TT (N=125)		MCC-CRM (N=111)		Total (N=236)	
		Observed response		Observed response		Observed response	
Antigen	**Endpoint**	**s/n or n**	**[95% CI] [1]**	**s/n or n**	**[95% CI] [1]**	**s/n or n**	**[95% CI] [1]**
PRP	% with titres ≥0.15 µg/mL	91/93	97.8 [92.4, 99.7]	82/82	100 [95.6, 100]	173/175	98.9 [95.9, 99.9]
	GMT (µg/mL)		6.44 [4.70, 8.83]		8.21 [6.08, 11.09]		7.22 [5.81, 8.97]
HBsAg	% with titres ≥10 mIU/mL	90/93	96.8 [90.9, 99.3]	79/82	96.3 [89.7, 99.2]	169/175	96.6 [92.7, 98.7]
	GMT (mIU/mL)		195.1 [150.7, 252.7]		247.7 [186.3, 329.3]		218.2 [180.4, 264.0]
Diphtheria	% with titres ≥0.01 IU/mL	125/125	100 [97.1, 100]	104/104	100 [96.5, 100]	229/229	100 [98.4, 100]
	% with titres ≥0.1 IU/mL	85/125	68.0 [59.1, 76.1]	77/104	74.0 [64.5, 82.1]	162/229	70.7 [64.4, 76.5]
	GMT (IU/mL)		0.198 [0.165, 0.237]		0.220 [0.181, 0.268]		0.208 [0.182, 0.237]
Tetanus	% with titres ≥0.01 IU/mL	122/122	100 [97.0, 100]	105/105	100 [96.5, 100]	227/227	100 [98.4, 100]
	% with titres ≥0.1 IU/mL	122/122	100 [97.0, 100]	105/105	100 [96.5, 100]	227/227	100 [98.4, 100]
	GMT (IU/mL)		1.03 [0.90, 1.17]		0.95 [0.82, 1.10]		0.99 [0.90, 1.09]
Pertussis PT	% with seroresponse [2]	99/100	99.0 [94.6, 100]	75/75	100 [95.2, 100]	174/175	99.4 [96.9, 100]
	GMT (EU/mL)	112	131.5 [117.2, 147.6]	89	133.3 [118.3, 150.2]	201	132.3 [121.8, 143.7]
Pertussis FHA	% with seroresponse [2]	91/100	91.0 [83.6, 95.8]	67/74	90.5 [81.5, 96.1]	158/174	90.8 [85.5, 94.7]
	GMT (EU/mL)	112	50.4 [44.8, 56.6]	88	50.1 [43.7, 57.4]	200	50.2 [46.0, 54.9]
Pertussis PRN	% with seroresponse [2]	95/100	95.0 [88.7, 98.4]	66/73	90.4 [81.2, 96.1]	161/173	93.1 [88.2, 96.4]
	GMT (EU/mL)	112	90.4 [73.2, 111.7]	87	106.8 [83.7, 136.3]	199	97.2 [83.0, 114.0]
Pertussis FIM	% with seroresponse [2]	96/100	96.0 [90.1, 98.9]	72/75	96.0 [88.8, 99.2]	168/175	96.0 [91.9, 98.4]
	GMT (EU/mL)	112	401.7 [339.4, 475.5]	89	441.7 [363.2, 537.2]	201	419.0 [369.0, 475.6]

RESULTS (*Cont.*):

Table S9: Summary of PR5I Antigen Responses Post-Dose 3 of PR5I (N=236) (Per Protocol Set – Part I) (*Cont.*)

		MCC-TT (N=125)		MCC-CRM (N=111)		Total (N=236)	
		Observed response		Observed response		Observed response	
Antigen	**Endpoint**	**s/n**	**[95% CI] [1]**	**s/n**	**[95% CI] [1]**	**s/n**	**[95% CI] [1]**
Poliovirus Type 1	% with titres ≥1:8 dil	114/114	100 [96.8, 100]	95/95	100 [96.2, 100]	209/209	100 [98.3, 100]
	GMT (dil)		214.0 [164.9, 277.7]		257.9 [193.8, 343.1]		232.9 [192.4, 282.0]
Poliovirus Type 2	% with titres ≥1:8 dil	106/106	100 [96.6, 100]	89/89	100 [95.9, 100]	195/195	100 [98.1, 100]
	GMT (dil)		385.2 [288.2, 514.9]		400.6 [290.6, 552.3]		392.2 [316.8, 485.5]
Polio Type 3	% with titres ≥1:8 dil	90/90	100 [96.0, 100]	74/74	100 [95.1, 100]	164/164	100 [97.8, 100]
	GMT (dil)		502.2 [370.2, 681.4]		405.1 [284.9, 576.0]		455.8 [362.6, 573.1]

CI = confidence interval; GMT = geometric mean titre; n = number of subjects included in the analysis; s = number of subjects with the response.
[1] The 95% CI for response rate is based on the exact binomial method by D. COLLETT. The 95% CI for GMT is based on the t-distribution of the natural log-transformed antibody titre.
[2] Pertussis seroresponse was defined as: (1) if the pre-vaccination antibody concentration was < lower limit of quantification (LLOQ), then the post-vaccination antibody concentration was to be ≥ LLOQ; (2) if the prevaccination antibody concentration was ≥ LLOQ, then the post-vaccination antibody concentration was to be ≥ pre-immunisation levels.
Source: Listing 16.2.6.a

Part II

Descriptive statistics regarding **PRP and MCC antigen responses** before and 1 month after a combined Hib-MCC vaccine dose based on the Part II PPS are provided in Table S10.

For Hib (PRP) antigen, results were comparable between the 2 vaccine groups. On the combined analysis across vaccine groups, at 12 months of age, before the booster dose with the combined Hib-MCC vaccine, the SPR to Hib (PRP) (i.e. proportion of subjects with an anti-PRP titre ≥0.15 µg/mL) was high (94.7%). At 13 months of age, 1 month after the booster dose, all the subjects were seroprotected (anti-PRP titre ≥0.15 µg/mL) and 99.5% of the subjects reached a titre ≥1.0 µg/mL.

For MCC antigen, results differed according to the vaccine group. At 12 months of age, before the booster dose with the combined Hib-MCC vaccine, 83.1% of the subjects in the MCC-TT group were still seroprotected (i.e. proportion of subjects with an anti-MCC titre ≥1:8 dil) as compared to 40.4% in the MCC-CRM group. At 13 months of age, 1 month after the booster dose, the SRP was 100% in the MCC-TT group and 97.3% in the MCC-CRM group. Based on non-overlapping CIs, the pre- and post-booster GMTs were higher in the MCC-TT group (50.3 and 3257.9 dil, respectively) than in the MCC-CRM group (8.7 and 580.8 dil, respectively).

Results based on the Part II FAS were comparable.

RESULTS (*Cont.*):

Table S10: Summary of MCC and PRP Antigen Responses Per Dose – Part II (N=222) (Per Protocol Set - Part II)

		MCC-TT (N=111)		MCC-CRM (N=111)		Total (N=222)	
Time point	**Endpoint**	**s/n**	**Observed response [95% CI] [1]**	**s/n**	**Observed response [95% CI] [1]**	**s/n**	**Observed response [95% CI] [1]**
Hib (PRP)							
Pre-Hib-MCC vaccine	% with titre ≥0.15 µg/mL	77/82	93.9 [86.3, 98.0]	83/87	95.4 [88.6, 98.7]	160/169	94.7 [90.1, 97.5]
	% with titre ≥1.0 µg/mL	45/82	54.9 [43.5, 65.9]	49/87	56.3 [45.3, 66.9]	94/169	55.6 [47.8, 63.2]
	GMT (µg/mL)		1.09 [0.81, 1.45]		1.18 [0.90, 1.55]		1.14 [0.93, 1.38]
Post-Hib-MCC vaccine	% with titre ≥0.15 µg/mL	110/110	100 [96.7, 100]	106/106	100 [96.6, 100]	216/216	100 [98.3, 100]
	% with titre ≥1.0 µg/mL	109/110	99.1 [95.0, 100]	106/106	100 [96.6, 100]	215/216	99.5 [97.4, 100]
	GMT (µg/mL)		100.19 [81.05, 123.86]		121.00 [101.11, 144.80]		109.91 [95.66, 126.28]
MCC							
Pre-Hib-MCC vaccine	% with titre ≥1:8 dil	74/89	83.1 [73.7, 90.2]	38/94	40.4 [30.4, 51.0]	112/183	61.2 [53.7, 68.3]
	% with titre ≥1:128 dil	36/89	40.4 [30.2, 51.4]	15/94	16.0 [9.2, 25.0]	51/183	27.9 [21.5, 35.0]
	GMT (dil)		50.3 [34.4, 73.4]		8.7 [5.9, 12.9]		20.5 [15.2, 27.5]
Post-Hib-MCC vaccine	% with titre ≥1:8 dil	109/109	100 [96.7, 100]	107/110	97.3 [92.2, 99.4]	216/219	98.6 [96.0, 99.7]
	% with titre ≥1:128 dil	108/109	99.1 [95.0, 100]	105/110	95.5 [89.7, 98.5]	213/219	97.3 [94.1, 99.0]
	GMT (dil)		3257.9 [2597.4, 4086.3]		580.8 [432.7, 779.5]		1370.1 [1102.4, 1702.9]

CI = confidence interval; n = number of subjects included in the analysis; s = number of subjects with the response.
[1] The 95% CI for response rate is based on the exact binomial method by D. COLLETT. The 95% CI for GMT is based on the t-distribution of the natural log-transformed antibody titre.
Source: Listing 16.2.6.b

Sanofi Pasteur MSD **CLINICAL STUDY REPORT**
SYNOPSIS

PR5I, suspension for injection, active immunisation against Diphtheria, Tetanus, Pertussis, Poliomyelitis (caused by poliovirus types 1, 2, and 3), infection caused by Hepatitis B virus, and against invasive disease caused by *Haemophilus influenzae* type b

RESULTS (*Cont.*):

Safety Results

ADVERSE EVENTS (PART I OF THE STUDY ONLY)

No notable differences were observed between the MCC-TT and MCC-CRM vaccine groups with regard to the frequency or nature of reported AEs.

During Day 1 to Day 15 following any infant doses, 97.9% (278/284) of subjects reported 1 or more AEs and 97.5% (277/284) of subjects reported 1 or more vaccine-related AEs.

Injection site AEs, which were always considered as vaccine-related (i.e. injection site reactions), were reported by 89.1% (253/284) of subjects following any infant doses.

Solicited injection site AEs (i.e. erythema, pain, and swelling that occurred between Day 1 and Day 5) were reported by 88.0% (250/284) of subjects after any doses of PR5I (3 doses) and by 69.0% (196/284) of subjects after any doses of MCC vaccine (2 doses). Erythema was the most frequently reported solicited injection site AE; it was reported by 68.0% (193/284) of subjects at PR5I injection site and by 51.1% (145/284) of subjects at MCC vaccine injection site.

Unsolicited injection site AEs (Day 1 to Day 15) were reported by 8.8% (25/284) of subjects after any doses with PR5I (3 doses) and by 2.8% (8/284) of subjects after any doses of MCC vaccine (2 doses). Bruising was the most frequently reported unsolicited injection site AE.

Most of injection site AEs were of mild intensity or had a size rating <2.5 cm. Injection site AEs usually lasted ≤5 days. No severe injection site reactions lasted >10 days.

Systemic AEs were reported by 96.5% (274/284) of subjects following any infant dose vaccination.

Solicited systemic AEs (i.e. pyrexia, vomiting, crying, somnolence, decreased appetite, and irritability that occurred between Day 1 and Day 5) were reported by 95.1% (270/284) of subjects and unsolicited systemic AEs (Day 1 to day 15) by 45.1% (128/284) of subjects. Most of systemic AEs were of mild or moderate intensity and lasted ≤5 days. Unsolicited systemic AEs usually lasted ≤10 days.

Vaccine-related systemic AEs (i.e. systemic AEs determined by the investigator as possibly, probably, or definitely related to the vaccine) were reported by 95.8% (272/284) of subjects after any dose vaccinations.

Solicited vaccine-related systemic AEs were reported by 95.1% (270/284) of subjects. Following any infant doses of PR5I (with/without PCV-13 or MCC vaccine), the most frequently reported vaccine-related solicited systemic AEs were irritability (84.5%, 240/284), crying (83.1%, 236/284), and somnolence (79.6%, 226/284).

Unsolicited vaccine-related systemic AEs were reported by 26.4% (75/284) of subjects.

Pyrexia (temperature ≥38.0°C) was experienced by 10.9% (31/284) of subjects during Day 1 to Day 5 following any infant dose. No severe hyperthermia (≥39.5°C) was reported. Pyrexia usually lasted ≤1 day.

A summary of clinical AEs that occurred after any infant dose vaccination is presented in Table S11.

Sanofi Pasteur MSD **CLINICAL STUDY REPORT**

SYNOPSIS

PR5I, suspension for injection, active immunisation against Diphtheria, Tetanus, Pertussis, Poliomyelitis (caused by poliovirus types 1, 2, and 3), infection caused by Hepatitis B virus, and against invasive disease caused by *Haemophilus influenzae* type b

RESULTS (*Cont.*):

Table S11: Summary of Clinical Adverse Events Following Any Infant Dose Vaccination (N=284) (Safety Set - Part I)

	MCC-TT (N=142)		MCC-CRM (N=142)		Total (N=284)	
	n	(%)	n	(%)	n	(%)
Number (%) of subjects:						
With no AE	2	(1.4)	4	(2.8)	6	(2.1)
With 1 or more AEs	140	(98.6)	138	(97.2)	278	(97.9)
1 or more vaccine-related AE	140	(98.6)	137	(96.5)	277	(97.5)
ISR (day 1 to day 15)	128	(90.1)	125	(88.0)	253	(89.1)
ISR at PR5I site (day 1 to day 15)	126	(88.7)	124	(87.3)	250	(88.0)
Solicited ISR (day 1 to day 5)	126	(88.7)	124	(87.3)	250	(88.0)
Injection site erythema	101	(71.1)	92	(64.8)	193	(68.0)
Injection site pain	90	(63.4)	94	(66.2)	184	(64.8)
Injection site swelling	73	(51.4)	67	(47.2)	140	(49.3)
Unsolicited ISR (day 1 to day 15)	9	(6.3)	16	(11.3)	25	(8.8)
ISR at MCC site (day 1 to day 15)	103	(72.5)	94	(66.2)	197	(69.4)
Solicited ISR (day 1 to day 5)	103	(72.5)	93	(65.5)	196	(69.0)
Injection site erythema	80	(56.3)	65	(45.8)	145	(51.1)
Injection site pain	59	(41.5)	65	(45.8)	124	(43.7)
Injection site swelling	51	(35.9)	40	(28.2)	91	(32.0)
Unsolicited ISR (day 1 to day 15)	4	(2.8)	4	(2.8)	8	(2.8)
Systemic AE (day 1 to day 15)	140	(98.6)	134	(94.4)	274	(96.5)
Solicited systemic AE (day 1 to day 5)	138	(97.2)	132	(93.0)	270	(95.1)
Unsolicited systemic AE (day 1 to day 15)	71	(50.0)	57	(40.1)	128	(45.1)
Vaccine-related systemic AE [1]	139	(97.9)	133	(93.7)	272	(95.8)
Solicited systemic AE (day 1 to day 5)	138	(97.2)	132	(93.0)	270	(95.1)
Crying	122	(85.9)	114	(80.3)	236	(83.1)
Decreased appetite	90	(63.4)	91	(64.1)	181	(63.7)
Irritability	125	(88.0)	115	(81.0)	240	(84.5)
Pyrexia	16	(11.3)	15	(10.6)	31	(10.9)
Somnolence	116	(81.7)	110	(77.5)	226	(79.6)
Vomiting	57	(40.1)	69	(48.6)	126	(44.4)
Unsolicited systemic AE (day 1 to day 15)	38	(26.8)	37	(26.1)	75	(26.4)
SAE (day 1 to day 15)	6	(4.2)	4	(2.8)	10	(3.5)
Vaccine-related SAE	0	(0.0)	1	(0.7)	1	(0.4)
Death	0	(0.0)	0	(0.0)	0	(0.0)
Withdrawn due to AE [2]	0	(0.0)	0	(0.0)	0	(0.0)
Withdrawn due to vaccine-related SAE [1,2]	0	(0.0)	0	(0.0)	0	(0.0)

AE = Adverse event; ISR = Injection site reaction (vaccine related IS AE); N = Number of subjects vaccinated; SAE = serious adverse event
The AEs are collected up to 15 days post any vaccination, SAEs that lead to death or are vaccine-related are collected at any time during the study. Summary includes SAE which occurred up to Visit 4. Percentages are based on the number of subjects in the population.
[1] Determined by the investigator to be related to the vaccine.
[2] Study medication withdrawn.
Source: Listing 16.2.7.a, Listing 16.2.7.b

Sanofi Pasteur MSD **CLINICAL STUDY REPORT**

SYNOPSIS

PR5I, suspension for injection, active immunisation against Diphtheria, Tetanus, Pertussis, Poliomyelitis (caused by poliovirus types 1, 2, and 3), infection caused by Hepatitis B virus, and against invasive disease caused by *Haemophilus influenzae* type b

RESULTS (*Cont.*):

DEATH, OTHER SERIOUS ADVERSE EVENTS, DISCONTINUATIONS DUE TO ADVERSE EVENTS (ENTIRE STUDY PERIOD)

There were no deaths and no withdrawals due to AEs during the whole study.

During Day 1 to Day 15 following any infant dose vaccination, 10 subjects reported a total of 11 SAEs: 6 subjects and 6 SAEs in the MCC-TT group and 4 subjects and 5 SAEs in the MCC-CRM group. Out of these 11 SAEs, 6 were classified in the '*infection and infestations*' System Organ Class and 9 were considered as unrelated to vaccination. The 2 SAEs considered as vaccine-related were transient severe abdominal pain and crying occurring concomitantly in 1 subject from the MCC-CRM group.

During Day 1 to Day 15 following the licensed toddler dose vaccination, no SAEs were reported.

No vaccine-related SAEs were reported outside of the Day 1 to Day 15 period following each vaccination.

CONCLUSIONS

The present immunogenicity and safety findings support the administration of PR5I as a 3-dose primary series given to healthy infants at 2, 3, and 4 months of age concomitantly with MCC vaccine.

The present findings also demonstrate that a 3-dose infant series of PR5I can be followed by a toddler dose of a combined Hib-MCC vaccine.

In healthy infants who received a accelerated 3-dose primary series at 2, 3, and 4 months of age with PR5I, the second and third doses given concomitantly with a MCC vaccine followed by a booster dose with a combined Hib-MCC vaccine at 12 months of age together with routine PCV-13 and MMR vaccinations, the following conclusions can be drawn:

- Post primary series, the post-Dose 2 SPR against MCC was acceptable for both the MCC-TT and MCC-CRM vaccines. Whatever the MCC vaccine used, the SPRs against MCC were high (titres ≥1:8 dil) after 2 doses (≥99.1%) but also after 1 dose (≥96.4%); SPRs were also high (≥97.3%) and comparable after the booster dose. However, post-dose 1 and post-dose 2 GMTs were higher in the MCC-TT than in the MCC-CRM group; these differences persisted at 12 months of age after the booster dose.
- PR5I induced a robust immune response against all disease antigens. Post-primary series, the SPR against Hib response was acceptable for the combined vaccine groups. The immune response was comparable to the responses observed in the pivotal controlled study which compared the accelerated 3-dose primary series with PR5I to a licensed control vaccine.
- PR5I was generally safe and well tolerated. The safety profile of PR5I was acceptable and consistent with that of the licensed vaccines.