

**Public Assessment Report
for paediatric studies submitted in accordance
with Article 46 of Regulation (EC) No1901/2006, as
amended**

**Covaxis
(Triaxis/Adacel)**

DE/W/0034/pdWS/005

**Marketing Authorisation Holder:
Sanofi Pasteur MSD GmbH**

Rapporteur:	Germany (PEI)
Finalisation procedure (day 90):	29 July 2016

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Covaxis (Triaxis/Adacel)
INN (or common name) of the active substance(s):	Diphtheria, Tetanus, Pertussis (acellular, component) Vaccine (adsorbed, reduced antigen(s) content)
MAH:	Sanofi Pasteur MSD GmbH
Currently approved Indication(s)	Covaxis is indicated for active immunization against tetanus, diphtheria, and pertussis in persons from 4 years of age as a booster following primary immunization. The use of Covaxis should be determined based on official local recommendations.
Pharmaco-therapeutic group (ATC Code):	J07AJ52
Pharmaceutical form(s) and strength(s):	Suspension for Injection

I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed.

II. RECOMMENDATION

No further action required

III. INTRODUCTION

On 16.03.16 the MAH submitted completed paediatric studies for Covaxis/Adacel, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Covaxis/Adacel and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the studies

The commercially available formulation of Covaxis (Triaxis/Adacel) was used in the studies.

IV.2 Clinical aspects

1. Introduction

The MAH submitted final reports for:

- Td536
- Td533

2. Clinical study(ies)

Td536: Immunogenicity and safety of the tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (SP306) given intramuscularly compared to Diphtheria and Tetanus toxoids adsorbed (DT) given subcutaneously in Japanese adolescents 11 – 12 years of age

➤ Description

Td536 was a Phase III, randomized, double-blind (recipient / observer-blind) immunogenicity and safety study of Adacel (referred to as SP306 or Tdap5 in the remainder of this document's section concerning study Td536) given intramuscularly, compared to Diphtheria and Tetanus toxoids adsorbed (DT) vaccine given subcutaneously in Japanese adolescents aged 11 or 12 years. This study was conducted from 01 March 2014 through 05 July 2014.

➤ Methods

A total of 534 subjects 11 – 12 years of age, who had been previously vaccinated with 4 doses of pediatric DTaP were randomized in a 2:1 ratio to receive a single dose of either :

- Group 1, SP306 0.5 ml given intramuscularly, or
- Group 2, a 0.1 mL dose of DT (DT BIK® or DT Biken) vaccine (from the Research Foundation for Microbial Disease of Osaka University) given subcutaneously.

Considering up to a 10% drop out rate, groups 1 and 2 were to include at least 320 and 160 evaluable subjects, respectively.

All subjects provided blood samples for immunogenicity assessment at baseline (pre-vaccination, Visit 1) and at Visit 2 (nominally, 28 days, window 28-35 days post vaccination). All assays for the primary endpoints were performed at the Sanofi Pasteur laboratory of Global Clinical Immunology (GCI) in Swiftwater, Pennsylvania, USA. GCI also performed the assays for the secondary immunogenicity endpoints, with the exception of Denka assays for PT and FHA antibodies. (See below.)

Subjects were monitored after vaccination for immediate adverse events (AEs) for 30 minutes; the following were also recorded: solicited injection site reactions and solicited systemic reactions for 7 days after vaccination; unsolicited AEs for 28 days after vaccination; and serious adverse events (SAEs) and medications/other vaccines received during the whole study period.

- Objective(s)

To demonstrate the non-inferiority of SP306 versus DT (DT Biken 0.1 mL) vaccine in terms of diphtheria and tetanus booster response rate (proportion of subjects with booster responses) and seroprotection rate (percentage of subjects with antitoxin concentrations ≥ 0.1 IU/mL) at 28 days (window 28-35 days) after one injection in Japanese adolescents 11-12 years of age.

To evaluate the immune response of SP306 against the pertussis antigens PT and FHA in terms of booster response rate (proportion of subjects with booster responses) at 28 days (window 28-35 days) after one injection in Japanese adolescents 11-12 years of age.

- Study design

Vaccination

All subjects received one dose of 0.5mL SP306 or 0.1mL DT Biken vaccine on Day 0.

Blood sampling

All subjects provided a pre-vaccination blood sample on Day 0 and a post-vaccination sample on Day 28 (+7 days) (7 mL sample at each visit).

Collection of safety data

Parents/legal representative(s) recorded information about solicited reactions and unsolicited AEs (including SAEs) in a diary card from Day 0 through Day 7 postvaccination, and recorded information about unsolicited AEs (including SAEs) from Day 8 until Visit 2.

The Investigator or authorized designee contacted subject's parent(s)/legal representative(s) by telephone on Day 8 (window, 6 -10 days) to remind them to record the Day 0-7 safety data in the diary card and to bring it with them to Visit 2.

- Outcomes/endpoints

Primary:

Diphtheria and tetanus

- Proportion of subjects with booster responses based on diphtheria and tetanus antitoxin concentration rises between pre-vaccination and 28 days (window, 28-35 days) post-vaccination specimens.

- A diphtheria booster response was defined as a ≥ 4 -fold rise in pre- to post-vaccination antitoxin concentration in a subject with a pre-vaccination antitoxin concentration ≤ 2.56 IU/mL or a ≥ 2 -fold rise in a subject with a pre-vaccination antitoxin concentration > 2.56 IU/mL
- A tetanus booster response was defined as a ≥ 4 -fold rise in pre- to post-vaccination antitoxin concentration in a subject with a pre-vaccination antitoxin concentration ≤ 2.7 IU/mL or a ≥ 2 -fold rise in a subject with a pre-vaccination antitoxin concentration > 2.7 IU/mL
- Proportion of subjects at 28 days (window, 28-35 days) post-vaccination with diphtheria and tetanus antitoxin concentrations ≥ 0.1 IU/mL (seroprotective level)

Pertussis

- Proportion of subjects with booster responses against pertussis antigens (PT and FHA) based on antibody concentration rises between pre-vaccination and 28 days (window, 28-35 days) post-vaccination specimens.
- For subjects whose pre-vaccination antibody concentrations were less than the lower limit of quantitation (LLOQ), a booster response was demonstrated if they had post-vaccination levels $\geq 4 \times \text{LLOQ}$
- For subjects whose pre-vaccination antibody concentrations were $\geq \text{LLOQ}$ but $< 4 \times \text{LLOQ}$, a booster response was demonstrated if they had a 4-fold rise (i.e., post-/pre-vaccination ≥ 4)
- For subjects whose pre-vaccination antibody concentrations were $\geq 4 \times \text{LLOQ}$, a booster response was demonstrated if they had a 2-fold rise (i.e., post-/pre-vaccination ≥ 2) (The LLOQs of the pertussis antibody assays as performed at GCI were 4 EU/mL for antibody to PT and 3 EU/mL for antibody to FHA.)

Secondary:

Diphtheria and tetanus

- Proportion of subjects with pre-vaccination diphtheria and tetanus antitoxin concentrations ≥ 0.1 IU/mL
- Proportion of subjects with pre-vaccination and 28 days (window, 28-35 days) post-vaccination diphtheria and tetanus antitoxin concentrations ≥ 0.01 , and ≥ 1.0 IU/mL
- Diphtheria and tetanus antitoxin geometric mean concentrations (GMC) at pre-vaccination and 28 days (window, 28-35 days) post-vaccination
- Diphtheria and tetanus antitoxin geometric mean fold rises (GMFR) between pre- and post-vaccination blood samples

Pertussis

- Proportion of subjects with booster responses against pertussis antigens (PRN and FIM) based on antibody concentration rise between pre-vaccination and 28 days (window, 28-35 days) post-vaccination specimens.
- For subjects whose pre-vaccination antibody concentrations were less than LLOQ, a booster response was demonstrated if they had post-vaccination levels $\geq 4 \times \text{LLOQ}$
- For subjects whose pre-vaccination antibody concentrations were $\geq \text{LLOQ}$ but $< 4 \times \text{LLOQ}$, a booster response was demonstrated if they had a 4-fold rise (i.e., post-/pre-vaccination ≥ 4)
- For subjects whose pre-vaccination antibody concentrations were $\geq 4 \times \text{LLOQ}$, a booster response was demonstrated if they had a 2-fold rise (i.e., post-/pre-vaccination ≥ 2) (The LLOQs of the pertussis antibody assays as performed at GCI were 4 EU/mL for antibody to both PRN and FIM.)
- Pertussis antibody (PT, FHA, PRN and FIM) GMC pre-vaccination and 28 days (window, 28-35 days) post-vaccination

- Pertussis antibody (PT, FHA, PRN and FIM) GMFR between pre- and post-vaccination blood samples
- Pertussis antibody (PT and FHA) measured by ELISA kit manufactured by DENKA SEIKEN Co., Ltd. in Japan:
Proportion of sero-positive – defined as antibody concentration ≥ 10 EU/mL – at pre-vaccination and 28 days (window, 28-35 days) post-vaccination
- GMC at pre-vaccination and 28 days (window, 28-35 days) post-vaccination
- GMFR between pre- and post-vaccination blood samples

Safety

- Occurrence, intensity, and relationship to vaccination of any unsolicited systemic AEs reported within the 30 minutes after vaccination
- Occurrence, time to onset, number of days of occurrence and intensity of solicited injection site and systemic reactions (terms prelisted in the subject's diary card and electronic case report form [eCRF]) occurring from Day 0 to Day 7 after vaccination
- Occurrence, nature (MedDRA preferred term), maximum intensity (for non-serious AEs only), and relationship to vaccination (for systemic AEs only), of unsolicited AEs up to 28 days after vaccination.
- Occurrence, nature (MedDRA preferred term), relationship to vaccination, seriousness, and outcome of SAEs occurring for the entire duration of each subject's involvement in the study.

- **Statistical Methods**

A total of 534 subjects were to be enrolled (group 1 [SP306]: 356 and group 2 [DT Biken]: 178, including 10% drop-out rate) with the aim to obtain at least 480 evaluable subjects. Based on the results of Study Td540 and Td519, it was expected that 95% of the subjects would have a booster response and 95% of the subjects would have a seroprotective antibody concentration levels (≥ 0.1 IU/mL) against both diphtheria and tetanus for both SP306 and DT Biken. It was also expected that 60% and 80% of the subjects would have a booster response against SP306's PT and FHA respectively. Given these expected results for the primary endpoints, the planned sample size of 480 evaluable subjects (320 SP306 and 160 DT Biken) allowed a global power of more than 90% to;

- Demonstrate non-inferiority of SP306 versus DT Biken in terms of booster response rate and seroprotection rate for diphtheria and tetanus with a 10% clinical non-inferiority margin and 2-sided type I error rate of 5%, and
- Ensure a lower bound of the 2-sided 95% confidence limits of booster response rate above preset level of 50% and 70% for PT and FHA respectively.

The planned sample size also allowed for identification of common AEs: A sample size of 320 evaluable subjects for SP306 allowed, with 95% probability, for the detection of an AE occurring with a frequency of 0.94 % or more, using the rule of threes.

➤ Results

- Recruitment/ Number analysed

Table 1 Overview of study population (source: Table 2, study report)

	SP306 (N=356)	DT (N=178)
Randomized subjects (All included subjects)	356 (100%)	178 (100%)
Full analysis set (FAS)	355 (99.7%)	178 (100%)
Per Protocol (PP) analysis set	350 (98.3%)	176 (98.9%)
Safety analysis set	356 (100%)	178 (100%)

One subject in the SP306 group discontinued due to poor compliance with the protocol.

Non-inferiority of Tdap5 to DT vaccine

Non-inferiority of Tdap5 against DT was shown for seroprotection.

Table 2 NI comparison for Tetanus and Diphtheria for 0.1IU/ml – Per protocol set (source: synopsis)

	SP306 (N=350)		DT (N=176)		Non-Inferiority Comparison	
	n/M (%)	(95% CI) ^a	n/M (%)	(95% CI) ^a	Difference (SP306 - DT)	(95% CI) ^b
Diphtheria	350/350 (100%)	(99.0; 100.0)	175/176 (99.4%)	(96.9; 100.0)	0.57%	(-0.61; 3.15)
Tetanus	350/350 (100%)	(99.0; 100.0)	176/176 (100%)	(97.9; 100.0)	0.00%	(-1.09; 2.14)

Booster responses

For diphtheria, the booster response rate of the subjects in the Tdap5 vaccine group (99.7%) was non-inferior to that in the DT vaccine group (98.3%); difference in booster response rate (Tdap5 - DT) = 1.42% (95% CI: -0.31; 4.61).

For tetanus, the booster response rate of the subjects in the Tdap5 vaccine group (100.0%) was non-inferior to that in the DT vaccine group (93.8%); difference in booster response rate (Tdap5 - DT) = 6.25% (95% CI: 3.32; 10.84).

Table 3 Seroprotection rate, GMCs and GMFRs – Per-protocol analysis set (source: synopsis)

Antibody tittier	SP306 (N=350)		DT (N=176)	
	Pre-Vaccination	Post-Vaccination	Pre-Vaccination	Post-Vaccination
Diphtheria				
Seroprotection rates				
≥ 0.01 IU/mL	97.4% (95.2 - 98.8)	100% (99.0 - 100.0)	97.7% (94.3 - 99.4)	99.4% (96.9 - 100.0)
≥ 0.1 IU/mL	46.6% (41.3 - 52.0)	100% (99.0 - 100.0)	46.6% (39.1 - 54.2)	99.4% (96.9 - 100.0)
≥ 1.0 IU/mL	4.3% (2.4 - 7.0)	98.0% (95.9 - 99.2)	5.1% (2.4 - 9.5)	97.7% (94.3 - 99.4)
GMCs (IU/mL)	0.10 (0.09 - 0.12)	8.64 (7.78 - 9.59)	0.10 (0.08 - 0.12)	10.08 (8.29 - 12.26)
GMFR	-	85.12 (75.06 - 96.52)	-	101.86 (84.61 - 122.63)
Tetanus				
Seroprotection rates				
≥ 0.01 IU/mL	100% (99.0 - 100.0)	100% (99.0 - 100.0)	99.4% (96.9 - 100.0)	100% (97.9 - 100.0)
≥ 0.1 IU/mL	77.1% (72.4 - 81.4)	100% (99.0 - 100.0)	77.8% (71.0 - 83.7)	100% (97.9 - 100.0)
≥ 1.0 IU/mL	7.1% (4.7 - 10.4)	100% (99.0 - 100.0)	8.0% (4.4 - 13.0)	98.9% (96.0 - 99.9)
GMCs (IU/mL)	0.25 (0.22 - 0.27)	26.15 (24.20 - 28.26)	0.24 (0.20 - 0.28)	7.58 (6.75 - 8.52)
GMFR	-	106.12 (96.36 - 116.86)	-	31.88 (26.68 - 38.09)

Prevaccination GMCs against the Pertussis antigens PT, PRN, FHA and FIM were similar in both groups. Post vaccination GMCs increased as expected only in the Tdap5-group.

Table 4 GMCs and GMFRs – Per-protocol analysis set (source: Table 17, study report)

Antibody tittier	SP306 (N=350)		DT (N=176)	
	Pre-Vaccination	Post-Vaccination	Pre-Vaccination	Post-Vaccination
PT				
GMCs (EU/mL)	6.27 (5.59 - 7.03)	23.83 (21.59 - 26.30)	6.15 (5.24 - 7.21)	6.07 (5.16 - 7.13)
GMFRs	-	2.94 (2.75 - 3.14)	-	0.75 (0.70 - 0.80)
FHA				
GMCs (EU/mL)	19.14 (17.01 - 21.55)	160.66 (149.49 - 172.66)	21.55 (18.41 - 25.22)	21.16 (18.17 - 24.65)
GMFRs	-	8.20 (7.43 - 9.03)	-	0.97 (0.91 - 1.02)
PRN				
GMCs (EU/mL)	7.02 (6.15 - 8.01)	129.59 (112.15 - 149.73)	8.20 (6.74 - 9.98)	7.94 (6.52 - 9.67)
GMFRs	-	14.31 (12.69 - 16.12)	-	0.78 (0.72 - 0.84)
FIM				
GMCs EU/mL)	3.43 (3.12 - 3.76)	233.01 (198.02 - 274.17)	3.68 (3.18 - 4.25)	3.63 (3.13 - 4.21)
GMFRs	-	42.03 (36.47 - 48.44)	-	0.62 (0.59 - 0.66)

**Table 5 Post-vaccination booster response rates for pertussis antigens (PT, FHA, PRN and FIM)
- Per-protocol analysis set (source: synopsis)**

	SP306 (N=350)	DT (N=176)
Post-Vaccination (Day 28)		
PT		
Subjects with booster response	137/350 (39.1%)	2/176 (1.1%)
95% CI ^a	(34.0% to 44.5%)	(0.1% to 4.0%)
FHA		
Subjects with booster response	333/350 (95.1%)	4/176 (2.3%)
95% CI ^a	(92.3% to 97.1%)	(0.6% to 5.7%)
PRN		
Subjects with booster response	316/350 (90.3%)	1/176 (0.6%)
95% CI ^a	(86.7% to 93.2%)	(0.0% to 3.1%)
FIM 2&3		
Subjects with booster response	331/350 (94.6%)	1/176 (0.6%)
95% CI ^a	(91.7% to 96.7%)	(0.0% to 3.1%)

Subjects whose pre-vaccination antibody concentrations are less than the lower limit of quantitation (LLOQ) demonstrate the booster response if they have post-vaccination levels $\geq 4 \times \text{LLOQ}$

Subjects whose pre-vaccination antibody concentrations are $\geq \text{LLOQ}$ but $< 4 \times \text{LLOQ}$ demonstrate the booster response if they have a 4-fold rise (i.e. post-/pre-vaccination ≥ 4)

Subjects whose pre-vaccination antibody concentrations are $\geq 4 \times \text{LLOQ}$ demonstrate the booster response if they have a 2-fold rise (i.e. post-/pre-vaccination ≥ 2)

Comparison of ELISA Kits

Measurement of the Pertussis antibodies PT and FHA with the DENKA ELISA Kit (Table 6) shows different results than the Swiftwater ELISA (Table 4).

Table 6 Pertussis (PT and FHA): Sero-positivity rates, GMCs and GMFRs measured by ELISA kit manufactured by DENKA SEIKEN Co. Ltd – Per-protocol analysis set

Antibody tittier	SP306 (N=350)		DT (N=176)	
	Pre-Vaccination	Post-Vaccination	Pre-Vaccination	Post-Vaccination
PT				
Sero-positivity rates (DENKA): ≥ 10 EU/mL:	60.6% (55.2 - 65.7)	98.0% (95.9 - 99.2)	67.6% (60.2 - 74.5)	64.2% (56.6 - 71.3)
GMCs (DENKA) (EU/mL)	11.71 (10.58 - 12.96)	33.03 (30.76 - 35.48)	12.32 (10.76 - 14.11)	12.62 (10.97 - 14.53)
GMFRs (DENKA)	-	2.80 (2.61 - 3.00)	-	1.02 (0.97 - 1.07)
FHA				
Sero-positivity rates (DENKA): ≥ 10 EU/mL:	86.3% (82.2 - 89.7)	100% (99.0 - 100.0)	88.1% (82.3 - 92.5)	92.0% (87.0 - 95.6)
GMCs (DENKA) (EU/mL)	27.39 (24.78 - 30.28)	141.13 (136.98 - 145.40)	31.55 (27.63 - 36.02)	32.89 (28.84 - 37.50)
GMFRs (DENKA)	-	5.15 (4.70 - 5.64)	-	1.04 (1.00 - 1.08)

The fold-increase for PT is similar to the one using the Swiftwater ELISA but for FHA it is lower (8.2 vs 5.15).

Also, the DENKA ELISA uses a different cut-off for seropositivity (>10 IU/ml) than is usually seen for the Swiftwater ELISA (usually 4 IU/ml for PT and FHA).

- Safety results

Two immediate reactions occurred in the Tdap5-group (vaso vagal syncope and abdominal pain). The Sponsor rates them unrelated to the vaccine but the assessor would classify the syncope to be related to the injection.

Local and systemic reactions were more frequent in the Tdap5 group.

Unsolicited AEs occurred in similar frequencies in both groups and were mostly infectious diseases.

No deaths, SAEs or AEs leading to discontinuation were seen in this study.

Table 7 Solicited injection site reactions, by maximum intensity during 7 days after vaccination - Safety Analysis Set (source: Table 21, study report)

Solicited reaction Maximum intensity n/M (%)	SP306 (N=356)	DT (N=178)
Any Solicited Injection Site Reaction		
All	296/356 (83.1%)	114/178 (64.0%)
Grade 1	216/356 (60.7%)	95/178 (53.4%)
Grade 2	72/356 (20.2%)	19/178 (10.7%)
Grade 3	8/356 (2.2%)	0/178
Injection Site Pain		
All	285/356 (80.1%)	86/178 (48.3%)
Grade 1	251/356 (70.5%)	81/178 (45.5%)
Grade 2	34/356 (9.6%)	5/178 (2.8%)
Grade 3	0/356	0/178
Injection Site Erythema		
All	72/356 (20.2%)	49/178 (27.5%)
Grade 1	33/356 (9.3%)	37/178 (20.8%)
Grade 2	34/356 (9.6%)	12/178 (6.7%)
Grade 3	5/356 (1.4%)	0/178
Injection Site Swelling		
All	72/356 (20.2%)	40/178 (22.5%)
Grade 1	33/356 (9.3%)	30/178 (16.9%)
Grade 2	34/356 (9.6%)	10/178 (5.6%)
Grade 3	5/356 (1.4%)	0/178

Rapporteur's comment:

Tdap5 was shown to be non-inferior to DT regarding seroprotection and titres against Tetanus and Diphtheria. This is unusual considering that the amount of diphtheria-antigen is so much higher in the DT vaccine.

Pertussis antibodies increased as expected in the Tdap5 group and a comparison with a different ELISA kit showed how important it is for comparisons to use similar validated assays. Regarding safety, a comparison of local reactogenicity showed that the intramuscular injection of Tdap5 was more reactogenic than the subcutaneous injection of DT. No new safety signals.

Td533 - ADACEL Post-Marketing Safety Surveillance in Korea

➤ Description

Td533 was conducted among 687 study vaccine recipients in 7 centers in South Korea from 23 June 2009 through 22 June 2015. This observational PMS study was designed to be conducted under real clinical practices in accordance with Korean Ministry of Food and Drug Safety (MFDS) Notification No. 2014-61 “Basic standard for reexamination of new drug” as a post-marketing commitment, per MFDS guidelines. Safety analysis was conducted on 659 subjects who had received 1 dose of ADACEL, with 24 subjects excluded for failed follow-up and 4 subjects excluded for off-label usage (i.e., age < 11 or > 64 years). Subjects were followed for 30 days. No efficacy evaluation was performed.

➤ Methods

- Objective(s)

To assess the following issues with respect to the safety of ADACEL™ (Adsorbed Diphtheria, Tetanus toxoids and component Pertussis combined Vaccine for Adult, hereinafter referred to as ‘the study vaccine’) administered under the real clinical practice.

- Study design

- Study population /Sample size

This study has planned sample size of at least 600 subjects in accordance with the Article 6.3 of “Basic standard for reexamination of new drug” (MFDS Notification No. 2014-61).

- Outcomes/endpoints

The study will collect the following events within 30 days post ADACEL™ administration:

- (1) Serious adverse events/adverse drug reactions
- (2) Unexpected adverse drug reactions: which are not reflected on ‘precautions for use’ (Refer to the attachment 1 ‘local product labeling’)
- (3) Already known adverse drug reactions
- (4) Non-serious adverse events
- (5) Adverse events due to abuse/misuse or drug interactions
- (6) Other safety-related data, including discovery of pregnancy

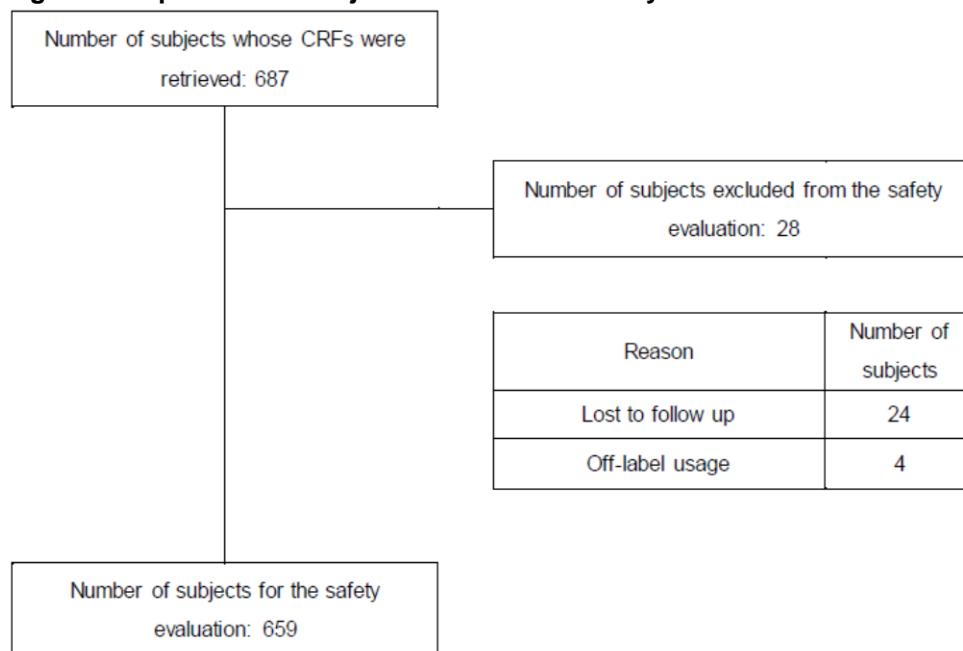
- Statistical Methods

Data collected from the participating centers will be analyzed and summarized for demographic and baseline characteristics and safety evaluation information. Exploratory analyses will be performed using descriptive statistics. Data will be presented for the complete population (all subjects who have received a dose of the study vaccine).

➤ Results

- Recruitment/ Number analysed

Figure 1 Disposition of subjects and numbers analyzed



- Baseline data

Table 8 Demographic characteristics (source: Table 1, study report)

Factor		No. of subject (%)
Gender	Male	205(31.11)
	Female	454(68.89)
	Total	659(100.00)
Pregnancy	Yes	0(0.00)
	No	425(93.61)
	Not applicable*	29(6.39)
	Total	454(100.00)
Age(year)	Mean±SD	24.38±13.51
	Min~Max	11.00~64.00
	<30 years	450(68.29)
	30 to <40 years	127(19.27)
	40 to <50 years	37(5.61)
	50 to <60 years	30(4.55)
	≥60 years	15(2.28)
	Total	659(100.00)
Pediatric population	<12 years	186(28.22)
	≥12 years	473(71.78)
	Total	659(100.00)
Weight(kg) [†]	N	637
	Mean±SD	52.59±12.08
	Min~Max	25.00~92.00
In/Out	In-patient	2(0.30)
	Out-patient	657(99.70)
	Total	659(100.00)

Table 9 Medical background (source: Table 2, study report)

Factor		No. of subject (%)
1. Current medical conditions	Yes	155(23.52)
	No	504(76.48)
	Total	659(100.00)
1) Renal disease	Yes	3(0.46)
	No	656(99.54)
	Total	659(100.00)
2) Hepatic disease	Yes	8(1.21)
	No	651(98.79)
	Total	659(100.00)
2. Past medical history	Yes	137 (20.79)
	No	522(79.21)
	Total	659(100.00)
3. Allergic history	Yes	21 (3.19)
	No	638(96.81)
4. Primary vaccination for pediatric DTP	Complete in schedule	272 (41.27)
	Not complete	10(1.52)
	Unknown	377(57.21)
	Total	659(100.00)
5. Past vaccination	Yes	26 (3.95)
	No	633(96.05)
	Total	659(100.00)
6. Simultaneous vaccination	Yes	128 (19.42)
	No	531(80.58)
	Total	659(100.00)
7. Concomitant medication	Yes	144 (21.85)
	No	515(78.15)
	Total	659(100.00)

Table 10 Distribution of simultaneous vaccination (source: Table 6, study report)

Simultaneous vaccination	No. of subject(%)
Yes	128(19.42)
No	531(80.58)
Total	659(100.00)
Type of Simultaneous vaccination*	No. of subject(%),[No. of vaccination]
Japanese encephalitis	52(7.89),[52]
Hepatitis A	39(5.92),[39]
Influenza	13(1.97),[13]
Hepatitis B	12(1.82),[12]
Invasive infection(bacteremia·pneumonia·meningitis) [†]	5(0.76),[5]
Varicella	3(0.46),[3]
Cervical cancer	3(0.46),[3]
Typhoid	2(0.30),[2]
Meningococcus diseases	2(0.30),[2]
Polio	1(0.15),[1]
Total	128(19.42),[132]

- Safety results

Table 11 Summary of Adverse Events (source: Table 9, study report)

AE/ADR	Adverse Events		Adverse Drug Reactions	
	No. of Subject With AE(%), [Case]	95% C.I.	No. of Subject With ADR(%), [Case]	95% C.I.
Adverse Events	168(25.49), [338]	[22.17, 28.82]	135(20.49), [262]	[17.40, 23.57]
Serious Adverse Events	1(0.15), [1]	[0.00, 0.45]	0(0.00), [0]	[0.00, 0.56]
Unexpected Adverse Events	68(10.32), [107]	[8.00, 12.64]	33(5.01), [41]	[3.34, 6.67]

SAEs:

One SAE occurred (knee pain) that was not considered related to the vaccination.

Immediate reactions:

No immediate reactions were reported.

AEs:

Only one severe graded local swelling was seen and one case of severe graded fever and malaise. Otherwise, AEs were graded mostly as mild.

For details on unexpected and all AEs please refer to Table 12 and Table 13.

A subgroup analysis of renal and hepatic disease subjects showed a higher rate of adverse reactions in these groups.

Comparison between the age groups showed the highest rate of AEs (irrespective of causality) in >60y of age and the lowest in the youngest age group <12 y of age.

Overall, no new safety issues were seen.

Table 12 Frequency distribution for adverse events/ adverse drug reactions (source: Table 12, study report)

AE/ADR	AE No. of subject(%)	ADR No. of subject(%)
Yes	168(25.49)	135(20.49)
No	491(74.51)	524(79.51)
Total	659(100.00)	659(100.00)
Type of AE/ADR*	No. of subject with AE (%),[Case]	No. of subject with ADR (%),[Case]
Application site disorders	127(19.27),[202]	127(19.27),[202]
Injection-site pain [†]	108(16.39),[108]	108(16.39),[108]
Injection-site erythema [†]	46(6.98),[46]	46(6.98),[46]
Injection-site swelling [†]	42(6.37),[42]	42(6.37),[42]
Injection-site itching [†]	5(0.76),[5]	5(0.76),[5]
Injection-site bruising [†]	1(0.15),[1]	1(0.15),[1]
Musculo-skeletal system disorders	26(3.95),[27]	23(3.49),[24]
Myalgia	26(3.95),[26]	23(3.49),[23]
Arthralgia	1(0.15),[1]	1(0.15),[1]
Respiratory system disorders	25(3.79),[34]	-
Bronchitis	11(1.67),[12]	-
Rhinitis	6(0.91),[6]	-
Coughing	3(0.46),[3]	-
Rhinorrhoea	3(0.46),[3]	-
Nasopharyngitis	2(0.30),[2]	-
Pharyngitis	2(0.30),[2]	-
Throat sore	2(0.30),[2]	-
Asthma	1(0.15),[1]	-
Nasal obstruction [†]	1(0.15),[1]	-
Sputum [†]	1(0.15),[1]	-
Tonsillitis	1(0.15),[1]	-
Body as a whole - general disorders	25(3.79),[26]	19(2.88),[20]
Malaise	14(2.12),[14]	14(2.12),[14]
Fever	7(1.06),[7]	4(0.61),[4]
Influenza [†]	2(0.30),[2]	-
Knee pain [†]	1(0.15),[1]	-
Pain axillary	1(0.15),[1]	1(0.15),[1]
Purulent discharge	1(0.15),[1]	1(0.15),[1]
Gastro-intestinal system disorders	20(3.03),[21]	1(0.15),[2]
Gastritis	8(1.21),[8]	-
Gastritis acute	3(0.46),[3]	-
Gastroenteritis	3(0.46),[3]	-
Diarrhoea	2(0.30),[2]	-
Enteritis	2(0.30),[2]	-
Dyspepsia	1(0.15),[1]	-
Nausea	1(0.15),[1]	1(0.15),[1]
Vomiting	1(0.15),[1]	1(0.15),[1]
Central & peripheral nervous system disorders	15(2.28),[17]	12(1.82),[13]
Headache	13(1.97),[14]	11(1.67),[11]
Dizziness	3(0.46),[3]	2(0.30),[2]
Skin and appendages disorders	5(0.76),[6]	1(0.15),[1]
Dermatitis atopic	1(0.15),[1]	-
Furuncle (excl genital)	1(0.15),[1]	-
Itching	1(0.15),[1]	1(0.15),[1]
Rash	1(0.15),[1]	-
Rash impetiginous	1(0.15),[1]	-
Sweating increased	1(0.15),[1]	-
Vision disorders	2(0.30),[2]	-
Allergic conjunctivitis	1(0.15),[1]	-
Conjunctivitis	1(0.15),[1]	-
Liver and biliary system disorders	1(0.15),[2]	-
ALT increased	1(0.15),[1]	-
AST increased	1(0.15),[1]	-
Resistance mechanism disorders	1(0.15),[1]	-
Hand-foot-and-mouth disease [†]	1(0.15),[1]	-
Total	168(25.49),[338]	135(20.49),[262]

Table 13 Frequency distribution for unexpected adverse events/ adverse drug reactions (source: Table 11, study report)

AE/ADR	AE No. of subject(%)	ADR No. of subject (%)
Yes	68(10.32)	33(5.01)
No	591(89.68)	626(94.99)
Total	659(100.00)	659(100.00)
Type of AE/ADR*	No. of subject with AE (%) ,[Case]	No. of subject with ADR (%) ,[Case]
Musculo-skeletal system disorders	26(3.95),[26]	23(3.49),[23]
Myalgia [‡]	26(3.95),[26]	23(3.49),[23]
Respiratory system disorders	25(3.79),[34]	-
Bronchitis	11(1.67),[12]	-
Rhinitis	6(0.91),[6]	-
Coughing	3(0.46),[3]	-
Rhinorrhoea	3(0.46),[3]	-
Nasopharyngitis	2(0.30),[2]	-
Pharyngitis	2(0.30),[2]	-
Throat sore	2(0.30),[2]	-
Asthma	1(0.15),[1]	-
Nasal obstruction [†]	1(0.15),[1]	-
Sputum [†]	1(0.15),[1]	-
Tonsillitis	1(0.15),[1]	-
Body as a whole - general disorders	17(2.58),[18]	15(2.28),[16]
Malaise [‡]	14(2.12),[14]	14(2.12),[14]
Influenza [†]	2(0.30),[2]	-
Pain axillary	1(0.15),[1]	1(0.15),[1]
Purulent discharge	1(0.15),[1]	1(0.15),[1]
Gastro-intestinal system disorders	17(2.58),[17]	-
Gastritis	8(1.21),[8]	-
Gastritis acute	3(0.46),[3]	-
Gastroenteritis	3(0.46),[3]	-
Enteritis	2(0.30),[2]	-
Dyspepsia	1(0.15),[1]	-
Skin and appendages disorders	3(0.46),[4]	-
Dermatitis atopic	1(0.15),[1]	-
Furuncle (excl genital)	1(0.15),[1]	-
Rash impetiginous	1(0.15),[1]	-
Sweating increased	1(0.15),[1]	-
Central & peripheral nervous system disorders	3(0.46),[3]	2(0.30),[2]
Dizziness	3(0.46),[3]	2(0.30),[2]
Vision disorders	2(0.30),[2]	-
Allergic conjunctivitis	1(0.15),[1]	-
Conjunctivitis	1(0.15),[1]	-
Liver and biliary system disorders	1(0.15),[2]	-
ALT increased	1(0.15),[1]	-
AST increased	1(0.15),[1]	-
Resistance mechanism disorders	1(0.15),[1]	-
Hand-foot-and-mouth disease [†]	1(0.15),[1]	-
Total	68(10.32),[107]	33(5.01),[41]

* overlapping counting, WHOART 092

[†] MedDRA 17.0 Lowest Level Term (In case WHOART is not available)

[‡] Both Myalgia and Malaise are included in the Sanofi Pasteur Safety Guideline as preferred terms for solicited reactions. Myalgia in earlier studies was referred to as Body Ache or Muscle Weakness; these 3 terms are included together in the solicited adverse reactions table of the Adacel™ Company Core Data Sheet (CCDS). Malaise in earlier studies was referred to as Tiredness; these 2 terms are listed together in that same table of the Adacel™ CCDS. However, neither Myalgia nor Malaise are included in the current Adacel™ product leaflet in Korea, that is why they are being dealt with in this section of the PMS study report.

Rapporteur's comment:

This study does not add any new information to the safety profile of this vaccine as laid down in the SmPC.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

The information provided from the two studies repeats results known from previous studies. No new safety signals are reported.

➤ Recommendation

No further action required

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

Not applicable