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

< Typhim Vi > <(Salmonella Typhimurium)>

AT/W/0017/pdWS/001-002

Marketing Authorisation Holder: Sanofi Pasteur MSD

Rapporteur:	Austria
Start of the procedure (day 0):	28.09.2017
Deadline for Rapporteuer´s preliminary paediatric assessment report (PPdAR) (day 70):	07.12.2017
Deadline for CMS´s comments (day 85):	22.12.2017
Date re-start of procedure (day 90):	27.12.2017
Finalisation procedure (day 120):	13.07.2018

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Typhim Vi
INN (or common name) of the active substance(s):	Salmonella Typhimurium
MAH:	Sanofi Pasteur MSD
Currently approved Indication(s)	TYPHIM Vi is indicated for active immunisation against typhoid fever caused by Salmonella enterica serovar typhi, S.typhi in adults and children 2 years of age or older.
Pharmaco-therapeutic group (ATC Code):	J07AP03, Typhoid, purified polysaccharide antigen
Pharmaceutical form(s) and strength(s):	0,05 mg/ml; Solution for injection in pre-filled syringe

I. EXECUTIVE SUMMARY

SmPC and PIL changes are proposed in sections 4.8 of the SmPC and section 4 of the PIL. The agreed wording is given in section V.

II. RECOMMENDATION

Section 4.8 of the SmPC and Section 4 of the PIL will be updated according to the agreed wording. A Type II Variation is requested from the MAH within 2 months after publication of the PAR. The SmPC and PIL changes are indicated in section V of this report.

III. INTRODUCTION

The MAH submitted 2 completed paediatric studies for Typhim Vi vaccine, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.
Furthermore, a pooled analysis on 6 studies was provided, which according to the MAH allowed a more precise evaluation of the ARs of Typhim Vi.

A short critical expert overview has also been provided including a proposal for changes in the SmPC section 4.8 and the respective section of the PIL.

The MAH stated that the submitted paediatric studies do not influence the benefit risk Typhim Vi vaccine. However changes in section 4.8 of the SmPC were recommended. After assessment of the submitted studies and acceptance of the recommendations, the MAH adopted the proposal to be incorporated in the SmPC and the respective section of the PIL which re. The agreed wording is given in section V.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study(ies)

Typhim Vi vaccine was the treatment used in the submitted studies, but the formulation of this product at the time of the studies is not provided by the applicant.

IV.2 Clinical aspects

1. Introduction

The MAH submitted final reports for:

Study Number (Study Code)	Study title	Study Design, Country and Period	Safety objectives
Study 29 (CYD22 -NCT00875524)	Tetravalent Dengue Vaccine in Healthy Subjects Aged 2 to 45 Years in Vietnam	Phase II randomized, blind-observer, controlled, monocenter trial Vietnam 2009-2014	To evaluate the safety of each vaccination with CYD dengue vaccine in the 4 age cohorts
Study 30 (TYP31)	Immunogenicity and Safety of a Single	Phase III, multi-center trial	To describe the safety profile of a single dose of

	Dose of SP093 Typhoid Vi polysaccharide Vaccine in Japanese Subjects	Japan 2012	SP093 vaccine up to 28 days after vaccination, in subjects aged 2 years and above.
Study 11 (YF18901)	Combined immunization with live attenuated yellow fever (YF) vaccine and Typhim vaccine (Vi) in adults	Phase III, controlled, randomized study Austria 1990-1991	To compare the safety of Vi and YF when administered separately or in a combined form
Study 12 (AVI01398)	Immunogenicity and safety of a hepatitis A (HA) and typhoid fever combined vaccine: comparison between the dual-chamber presentation and the concomitant administration into 2 different sites	randomized, controlled The Netherlands/France 1998-2002	To describe immediate, local and systemic reactogenicity within 28 days after vaccination.
Study 14 (MTA11)	Immunogenicity and Safety of Typhoid Vi Vaccine when Administered Concomitantly with an Experimental Tetravalent (A, C, Y, and W-135) Meningococcal Diphtheria Toxoid Conjugate Vaccine (TetraMenD) in Adults in the U.S.	Randomized, doubleblind, active-controlled, multicenter USA 2002-2003	To describe the safety profile (immediate reactions, solicited local and systemic reactions, and unsolicited AEs and serious adverse events [SAEs]) for each treatment group
Study 15 (CYD05)	Safety of ChimeriVax™ Dengue Tetravalent Vaccine in Subjects Aged 2 to 45 Years in the Philippines	Phase II, randomized, controlled, monocenter study Philippines 2006-2011	To evaluate the safety of each vaccination with chimeric yellow fever dengue (CYD dengue) vaccine in the 4 age cohorts

Table 1: Pediatric Subjects in the Pooled Safety Analysis by Study

Study	Children 2-11 years	Adolescents 12-17 years	All Pediatric Subjects <18 years
Study 12 (AVI01398)	-	1	1
Study 15 (CYD05)	24	12	36
Study 29 (CYD22)	39	9	48
Study 30 (TYP31)	5	7	12
Total	**68**	**29**	**97**

Study 29 (CYD22), Study 30 (TYP31), Study 12 (AVI01398) and Study 15 (CYD05) included subjects from ≤18 years of age. Therefore only these studies are described in detail in context to the paediatric Worksharing procedure.

2. Clinical study(ies)

*Study 29 - (**CYD22**): "Immunogenicity and Safety of Tetravalent Dengue Vaccine in Healthy Subjects Aged 2 to 45 Years in Vietnam"*

➢ Description

The clinical trial CYD22 was one of the first CYD dengue vaccine Phase II studies in Asia and included subjects previously exposed to Japanese encephalitis (JE) vaccine or infection. This study was conducted in Viet Nam, where dengue disease is endemo-epidemic. The aim of this study was to assess the immunogenicity and safety of CYD dengue vaccine in healthy subjects aged 2 to 45 years.

Trial period was from 2009 – 2014.

➢ Methods

- Main Objectives

  1) To describe the humoral immune response to dengue before and after each vaccination with CYD dengue vaccine in 4 age cohorts: adults (18 to 45 years), adolescents (12 to 17 years), and children (6 to 11 years and 2 to 5 years).

  2) To evaluate the safety of each vaccination with CYD dengue vaccine in the 4 age cohorts.

  3) To evaluate the persistence of Abs against dengue during 5 years after the first vaccination with CYD dengue vaccine in the 4 age cohorts.

  No immunogenicity testing for immune response to Typhim Vi vaccine was performed; only safety was assessed.

- Study design

  This was a randomized, blind-observer, controlled, monocenter, Phase II trial in 180 subjects in Viet Nam. Enrolment was sequential (per age cohort (adults (18 to 45 years), adolescents (12 to 17 years), and children (6 to 11 years and 2 to 5 years)).
  There were 3 vaccinations (Day [D] 0, D0 + 6 months, and D0 + 12 months) over 1 year followed by a 4-year follow-up. There were 2 groups of subjects:

  • Dengue Group received CYD dengue vaccine as the first, second, and third vaccinations.

  • Control Group received Meningococcal Polysaccharide Vaccine A + C as the first injection, a placebo (NaCl containing HSA) as the second injection, and *Typhoid Vi polysaccharide vaccine (Typhim Vi Vaccine)* as the third injection.

  A stepwise approach for the first vaccination was performed as follows:

  • Vaccination of adult subjects (18 to 45 years old).
  • Vaccination of adolescent subjects (12 to 17 years old) 14 ± 7 days later.
  • Safety review of D28 data of the adult and adolescent cohorts by the Safety Review Committee (composed of local team and Sponsor representatives); the Principal Investigator and the Sponsor made the final decision based on these safety data reviews to proceed with the first vaccination of children.
  • Vaccination of children (6 to 11 years old).
  • Vaccination of children (2 to 5 years old) 14 ± 7 days later.
  • Safety review of D28 data of the children cohorts (6 to 11 years old and 2 to 5 years old).

- Study population /Sample size

  Inclusion Criteria:
  1) Aged 2 to 45 years on the day of inclusion. (Scr.)
  2) Provision of Informed Consent/Assent Form signed by the subject (and/or by the parent or another legally acceptable representative for subjects <18 years). (Scr.)
  3) Subject (and parent/guardian for subjects <18 years) able to attend all scheduled visits and to comply with all trial procedures. (Scr. + V01)
  4) For a female subject of child-bearing potential, avoid becoming pregnant (use of an effective method of contraception or abstinence) for at least 4 weeks prior to the first vaccination, until at least 4 weeks after the last vaccination. (Scr. + V01)
  5) Subject in good health, based on medical history, physical examination and laboratory parameters. (Scr. + V01)

  Planned sample size: 180 subjects (120 subjects in the dengue group and 60 subjects in the control group).

- Treatments

  The following products were used in the study:

  • Dengue group: CYD dengue vaccine (previously known as ChimeriVax tetravalent dengue vaccine) for each of the 3 vaccinations in the dengue group

  • Control group: Meningococcal Polysaccharide Vaccine A + C (licensed vaccine) as the first vaccination, placebo (NaCl containing HSA) as the second vaccination, and Typhoid Vi polysaccharide vaccine (Typhim Vi licensed vaccine) as the third vaccination in the control group

  In each group, the products were administered subcutaneously using a 0-, 6-, and 12-month schedule

- Outcomes/endpoints

  Main Endpoints:

  Immunogenicity

  • Neutralizing Ab levels against each of the 4 parental dengue virus strains of CYD dengue vaccine constructs measured in sera collected from all the subjects before and 28 days after each vaccination, and each year during 5 years after the first vaccination (dengue plaque reduction neutralization test [PRNT]). No immunogenicity testing for immune response to Typhim Vi vaccine was performed; only safety was assessed.

  Safety

  Safety endpoints were:

  • Occurrence, nature, duration, intensity, action taken, and relationship to vaccination of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after each vaccination.

  • Occurrence, time to onset, number of days of occurrence, action taken, and intensity of solicited injection site reactions occurring up to 7 days after each vaccination.

  • Occurrence, time to onset, number of days of occurrence, action taken, and intensity of solicited systemic reactions occurring up to 14 days after each vaccination.

  • Occurrence, nature, time to onset, duration, intensity, action taken, and relationship to vaccination (for systemic AEs only) of unsolicited (spontaneously reported) AEs up to 28 days after each vaccination.

  • Occurrence of serious adverse events (SAEs) throughout the trial, as follows:

    • Up to 6 months after the last vaccination: all SAEs

• From 6 months after the last vaccination until the end of trial: only related and fatal (even if unrelated) SAEs

- Statistical Methods

  For this final CSR, all statistical analyses were descriptive and are presented with 95% confidence intervals (CIs) by using normal approximation for quantitative data and exact binomial distribution (Clopper-Pearson method) for proportions.
  All analyses were performed on each cohort separately as well as combined.
  Listings of safety data were produced after the adult (18 to 45 years) and adolescent (12 to 17 years) cohorts completed V04 (D28). These data were provided by the Sponsor's Data Management department to the Sponsor and the Investigator.
  An interim analysis of safety and immunogenicity was performed on unblinded data up to 28 days after the third vaccination and 1, 2, and 3 years after the third vaccination. A final analysis of safety and immunogenicity was performed on unblinded data after the end of the 4-year follow-up.

➢ Results

- Recruitment/ Number analysed

  A total of 180 subjects were randomized into 2 groups (120 subjects in the dengue group and 60 subjects in the control group). Among subjects included in the full analysis set (FAS), 166 (92.2%) subjects completed the study (112 subjects in the dengue group and 54 in the control group) and 14 (7.8%) subjects discontinued the study. Up to the 4-year follow-up after the third vaccination, the reasons for not completing the study were: SAE (i.e., 1 subject [1.7%] in the control group), non-compliance with the protocol (i.e., 4 subjects [3.3%] in the dengue group), lost to follow-up (i.e., 1 subject [0.8%] in the dengue group), or voluntary withdrawal not due to an AE (i.e., 3 subjects [2.5%] in the dengue group and 5 subjects [8.3%] in the control group).

  In the control group, 9 adolescents (12 to 17 years), 20 children (6 to 11 years) and 19 children (2 to 5 years) received one dose of Typhim Vi.

- Baseline data

  Subjects were classified into 4 age groups: in adults 18 to 45 years, in adolescents aged 12 to 17 years, in children aged 6 to 11 years, and in children aged 2 to 5 years. For both study groups combined, the overall male-to-female ratio was 51.7% (93/180) to 48.3% (87/180). Within each age group the male-to-female ratio was similar in both groups except in the control group where it was somewhat higher in children 2 to 5 years of age (65.0% [13/20] to 35.0% [7/20]) and children 6 to 11 years of age (65.0% [13/20] to 35.0% [7/20]); and in the dengue group where it was somewhat lower in adolescents 12 to 17 years of age (35.0% [7/20]) to 65.0% [13/20]. The 4 age groups were well balanced in terms of demographic characteristics. The mean age, height, weight, and body mass index (BMI) were similar in both study groups

- Efficacy results

  There were no main objectives for efficacy. No efficacy data were collected in this trial.

- Safety results

  Solicited Injection Site Reactions:
  Within 7 days after Typhim Vi vaccination in the control group, pain was the most frequently reported solicited injection site reaction in subjects aged 2 to 5 years, 6 to 11 years, and 12 to 17 years (21.1%, 35.0% and 77.8% of subjects, respectively). Erythema and swelling were less frequently reported, with ≤ 2 subjects per age strata.

All of the solicited injection site reactions were of Grade 1 intensity, except for 1 subject aged 12 to 17 years age who reported Grade 2 pain. The majority of solicited injection site reactions appeared within 3 days of vaccination and ranged from 1 to 3 days of occurrence.

Solicited Systemic Reactions:
Within 14 days after Typhim Vi vaccination in the control group, the most frequently reported reactions were: fever (10.5%) in children aged 2 to 5 years; headache (10.0%) in children aged 6 to 11 years; and headache (33.3%) in adolescents aged 12 to 17 years.
All of the solicited systemic reactions were of Grade 1 intensity, except for 1 subject aged 2 to 5 years with Grade 2 fever, and 1 subject aged 12 to 17 years with Grade 2 headache. The majority of solicited systemic reactions appeared within 3 days of vaccination and the number of days of occurrence ranged from 1 to 3 days.

Unsolicited Adverse Events:
No unsolicited AEs were reported at any time during the trial after the Typhim Vi vaccination for subjects aged 2 to 17 in the control group.

Serious Adverse Events (SAEs):
During the long-term follow-up, 1 fatal SAE was reported: a 13-year-old male subject had encephalitis post varicella 1012 days post vaccination with Typhim Vi vaccine. This SAE was assessed by the Investigator as not related to vaccination.

Assessor's/Rapporteur´s comment:
Overall, the sample size of subjects who received Typhim Vi was rather small (12 to 17 years (N=9) and 2 to 11 years (N=39)) and might mask small differences in safety signals. Furthermore, Typhim Vi was not the vaccine of primary interest, but was only applied as third vaccine in the control group, after a placebo vaccination has been used as second vaccine and Meningococcal Polysaccharide Vaccine A + C as the first vaccination in the control group. Therefore, the clinical relevance of the findings is rather limited.

From the safety results obtained, no new safety signals became apparent after the application of Typhim Vi. Within 14 days after vaccination with Typhim Vi, all systemic reactions were reported as Grade 1, with the exception of two Grade 2 reactions (fever and headache). All the solicited adverse reactions reported in adolescents and children are already listed in the SmPC except injection site swelling. However, the frequency of headache, malaise, and myalgia is higher in some age groups than the frequency "very rare" as reflected in the currently approved SmPC. The applicant however proposes changes in section 4.8 of the SmPC taking the results of the pooled analysis into account (see also "Discussion on clinical aspects" and "overall conclusion" below).

*Study 30 - (**TYP31**): "Immunognicity and Safety of a Single Dose of SP093 Typhoid Vi polysaccharide Vaccine Given in Japanese Subjects"*

- **Description**

This study assessed the immunogenicity and safety of a single dose of typhoid Vi polysaccharide vaccine (Typhim Vi) given in Japanese subjects aged 2 years and above to support registration of Typhim Vi in Japan in a total of 200 subjects.

Trial period was 2012.

- **Methods**

- *Primary Objectives*
  To describe the seroconversion rate (percentage of subjects with at least a 4-fold increase of their Vi antibody titer) between Day 0 before vaccination and Day 28 after

vaccination with TyphoidVi polysaccharide (SP093) vaccine in subjects aged 2 years and above.

Secondary Objectives

Safety:

To describe the safety profile of a single dose of SP093 vaccine up to 28 days after vaccination, in subjects aged 2 years and above.

Immunogenicity:

To describe the immune response following a single dose of SP093 vaccine in subjects aged 2 years and above.

- Study design

  This was a multi-center, Phase III, open-label, descriptive study to assess the immunogenicity and safety of a single dose of SP093 vaccine in subjects aged 2 years and above. A total of 200 subjects were enrolled.
  The study comprised of one age cohort or study group, ie, subjects aged 2 years and above.
  Each subject was followed for duration of 28 days (window of 28 to 35 days) after vaccination.

- Study population /Sample size

  A total of 200 subjects were planned to be enrolled (including 10% drop-out rate) with the aim to obtain a total of 180 evaluable subjects. Although there were no statistically powered hypotheses in this study, the number of subjects was designed to provide supportive immunogenicity and safety data of the study vaccine when administered as a single dose in Japanese population.

  Inclusion Criteria:
  1) Aged 2 years and above on the day of inclusion
  2). For subjects ≥20 years of age: Informed consent form has been signed and dated by the subjects
  For subjects 2 to 19 years of age: Informed consent form has been signed and dated by the parent(s) or other legally representative
  Also subjects 7 to 11 years of age provided assent and subjects 12 to 19 years of age provided written assent form
  3) Able to attend all scheduled visits/phone and to comply with all trial procedures
  4) For female subjects who have childbearing potential, use of an effective method of contraception from at least 4 weeks prior to vaccination until at least 4 weeks after vaccination

- Treatments

  SP093 vaccine was administered intramuscularly as a single 0.5 mL dose given at Visit 1.

- Outcomes/endpoints

  Primary Endpoints:
  Immunogenicity
  4-fold increase of Vi antibody titer (measured by ELISA) between Day 0 (before vaccination) and Day 28 (after vaccination) after a single dose of SP093 vaccine.

  Secondary Endpoints:

  Safety

- Occurrence, nature (MedDRA preferred term), duration, intensity, and relationship to vaccination of any unsolicited systemic adverse events (AEs) reported within 30 minutes after vaccination.
- Occurrence, time to onset, duration, and intensity of solicited injection site and systemic reactions (terms prelisted in the subject's diary card and case report form [CRF]) occurring from Day 0 to Day 7 after vaccination.
- Occurrence, nature (MedDRA preferred term), time to onset, duration, 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), time to onset, duration, relationship to vaccination and outcome of SAEs occurring for the entire duration of each subject's involvement in the study.

Immunogenicity
Vi antibody titers measured by ELISA in the serum specimens collected on Day 0 (before vaccination) and Day 28 (after vaccination) after a single dose of SP093 vaccine.

The following parameters were to be described:
• GMTs (and their 95% CIs) of Vi antibody titers at Day 0 pre vaccination and at Day 28 post vaccination

• Geometric mean of individual titers ratio (Day 28/ Day 0); GMTR

Reverse Cumulative Distribution Curves (RCDC) of individual antibody titers were also to be presented.

Depending on the immunogenicity assessment method chosen, the number and percentage of subjects with Vi antibody seroprotection level at Day 0 and at Day 28 was planned when seroprotection level and unit were to be confirmed. .

- Statistical Methods
  All analyses were descriptive; no hypotheses were tested.
  For the main parameters, 95% confidence intervals (CIs) of point estimates were calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for proportions.

  Sample size:
  Although there were no statistically powered hypotheses in this study, the number of subjects was designed to provide supportive immunogenicity and safety data of the study vaccine when administered as a single dose in Japanese population.

  Immunogenicity:
  The pre-set level of seroconversion rate was set to 75%. Assuming an expected seroconversion rate of 85%, a sample size of 180 evaluable subjects was calculated to ensure a 95%CI above the pre-set level with a power of 90%.

  Safety:
  The planned sample size allowed for identification of common AEs: A sample size of 180 evaluable subjects allowed, with 95% probability, for the detection of an AE occurring with a frequency of 1.6% or more, using the rule of threes.

➢ Results

- Recruitment/ Number analysed

  A total of 188 adults (aged from 18 to 57 years), 7 adolescents aged from 12 to 17 years (mean age: 15.6 years), and 5 children aged 2 to 11 years (mean age: 5.2 years).

Among the paediatric population, there were 4 males and 3 females for the adolescents and 4 males and 1 female for the children.

- Baseline data

  All included subjects were Asian/Oriental.
  In adults, out of the 188 included subjects, 116 were males and 72 were females. The mean age and weight of these subjects was 37.2 years (range, 19 - 57 years) and 61.05 kg (range, 38.2 – 119.7 kg), respectively. In adolescents, out of the 7 included subjects, 4 were males and 3 were females. The mean age and weight of the subjects was 15.6 years (range, 12 - 17 years) and 58.77 kg (range, 44.8 – 77.5 kg), respectively. In children, out of the 5 included subjects, 4 were males and 1 was female. The mean age and weight of the subjects was 5.2 years (range, 2 - 11 years) and 18.64 kg (range, 12.7 – 35.0 kg), respectively.

- Efficacy results
  No efficacy data were obtained in the trial.

- Safety results
  Safety:
  All subjects were observed for 30 minutes after injection, and no immediate unsolicited adverse events (AEs) were recorded.

  Solicited reactions (all and Grade 3 [i.e. severe]) recovered within 7 days after vaccination in adolescents and children are presented in Table 1.

Table 1: Solicited systemic reactions within 7 days after vaccine injection by n intensity - Safety Analysis Set

Solicited injection site reaction Maximum intensity	Adolescents [12-17] (N=7)	Children [2-11] (N=5)
Any Solicited Injection Site Reactions	**n/M (%)**	**n/M (%)**
All	6/7 (85.7%)	3/5 (60.0%)
Grade 3	0/7	0/5
Injection Site Pain		
All	6/7 (85.7%)	3/5 (60.0%)
Injection Site Erythema		
All	0/7	2/5 (40.0%)
Injection Site Swelling		
All	0/7	0/5
Any Solicited Systemic Reactions		
All	4/7 (57.1%)	2/5 (40.0%)
Grade 3	0/7	0/5
Fever		
All	0/7	1/5 (20.0%)
Headache		
All	0/7	0/5
Malaise		
All	0/7	0/5
Myalgia		
All	4/7 (57.1%)	1/5 (20.0%)

n: number of subjects experiencing the endpoint listed in the first column
M: number of subjects with available data for the relevant endpoint

In adolescents, 85.7% (6 of 7) of subjects experienced at least one solicited reactions: 85.7% experienced at least one injection site reaction and 57.1% (4 of 7) reported at least one solicited systemic reaction.

In children, 60.0% (3 of 5) of subjects experienced at least one solicited reaction; 60.0% experienced at least one injection site reaction and 40.0% (2 of 5) of subjects reported at least one solicited systemic reaction.

The solicited reaction reported in adolescents and was injection site pain (in 6 of 7 subjects) and myalgia (in 4 of 7 subjects). In children, in addition to injection site pain (in 3 of 5 subjects) and myalgia (in 1 of 5 subjects) other reactions such as erythema (in 2 of 5 subjects) and fever (in 1 of 5 subjects) were also reported.

None of the solicited reactions reported were of grade 3 intensity, in any of the two age groups.

In adolescents, all solicited reactions occurred within 3 days of vaccination and resolved within 3 days.

In children, all injection site reactions occurred within 3 days of vaccination and resolved within 3 days. Fever occurred between Day 4 and Day 7 and resolved within 7 days. Myalgia occurred between Day 0 and Day 3 and resolved within 3 days.

No unsolicited adverse events related to vaccine administration were reported during the study in adolescents and children.

No serious adverse events were reported for adolescents and children in this study.

Immunogenicity Results:

The data presented below are for the immunogenicity analysis set defined as all subjects who have received the study vaccine.

The number of subjects with ≥ 4- fold rise in anti-Vi antibody titers measured by ELISA for Vi antigen, and geometric means of titers (GMT) are presented in the following table:

Immunogenicity Criteria per Age – Immunology analysis set

Anti-Vi titers by ELISA (EU/mL)	**Adolescents [12-17] (N=7)**			**Children [2-11] (N=5)**		
Primary objective:	**n/M**	**%**	**95%CI**	**n/M**	**%**	**95%CI**
≥4-fold increase from D0 to D28:	6/7	85.7	(42.1; 99.6)	5/5	100.0	(47.8 100.0)

Secondary objectives:	**n**	**GMT**	**95%CI**	**n**	**GMT**	**95%CI**
GMTs Pre-vaccination - D0 (EU/mL)	7	10.2	2.9; 35.9	5	3.7	NC
GMT Post vaccination-D28 (EU/mL)	7	320.0	(230.6; 444.2)	5	501.7	(305.3; 824.5)
	n	**GMTR**	**95%CI**	**n**	**GMTR**	**95%CI**
GMTR D28/D0	7	31.4	(9.2; 107.9)	5	135.6	(82.5; 222.8)

N = immunology analysis set

M: number of subjects with available for the anti-Vi titer

In adolescents, 6 of 7 subjects (85.7%) showed ≥ 4- fold rise in Vi antibody titer on Day 28. One subject did not achieve ≥ 4-fold rise in Vi antibody titer on Day 28 due to the higher antibody titer of pre-vaccination. Seroconversion rate was inferior to 4-fold rise in one subject (pre-/postvaccination titers were 79.4 and 264.9, respectively i.e., corresponding to a 3.3 fold rise).

GMTs of anti-Vi antibody titers increased, between Day 0 and Day 28 from 10.2 to 320.0 in adolescents and 3.7 to 501.7 in children, respectively. Geometric mean of titer ratios (GMTRs) D28/D0 were 31.4 in adolescents and 135.6 in children, respectively.

Typhim Vi induced a robust immune response in all subjects, demonstrated by high proportion of subjects achieving a ≥ 4-fold rise in anti-Vi antibody titers and by increased GMTs compared to baseline values.

Assessor's/Rapporteur´s comment:

Overall, only a small number of paediatric patients were evaluated in this trial with only 12 paediatric subjects (12 to 17 years (N=7) and 2 to 11 years (N=5)) which may mask small differences in safety signals.

No efficacy data were obtained in the trial and there were no primary objectives for safety in the study.

Apart from the sufficient immune response observed during the study in adolescents and children, the safety results obtained indicate, that no new safety signals in the paediatric population became apparent after injection of Typhim Vi. A single injection was well tolerated in the Japanese paediatric population with no severe systemic reactions within the first 7 days after vaccination. Furthermore no unsolicited AEs assessed as related to the study vaccine were reported in adolescents and children. Very few solicited reactions were reported; mostly injection site pain and myalgia, and none were of Grade 3 intensity.

However, caution is required when interpretation these outcomes due to the very small sample size and the large imbalance in numbers between adults and paediatric subjects.

*Study 12 (**AVI01398**) - Immunogenicity and Safety of a Hepatitis A and Typhoid Fever Combined Vaccine: Comparison Between the Dual-Chamber Presentation and the Concomitant Administration into Two Sites of the Monovalent Hepatitis A and Typhoid Fever Vaccines* - Follow-up Report Including Data from Year 1 to Year 3 + 28 days (Complementary data to final report dated 3 September 1999)

Trial period was from 1998 – 2002.

- **Description**

Aventis Pasteur developed a combined vaccine against typhoid fever and hepatitis A (HA/Vi). It is presented in a liquid/liquid dual chamber syringe that contains:

- typhoid Vi polysaccharide vaccine component, identical composition of the licensed typhoid vaccine (TYPHIM Vi), but without phenol,
- inactivated hepatitis A vaccine component, identical to the currently licensed inactivated hepatitis A vaccine (AVAXIM).

This was the first evaluation of the by-pass formulation of the HA/Vi vaccine in man. The purpose of this trial was to compare the immunogenicity and safety of the combined vaccine to the concomitant administration of the two monovalent HA and Vi vaccines in subjects needing an initial vaccination against hepatitis A and a vaccination against typhoid fever.

- **Methods**

- *Objective*(s)

  Primary Objective:

  To demonstrate that the anti-HAV and anti-Vi antibody (Ab) responses 28* days after the administration of a single dose of a vaccine against hepatitis A and typhoid fever formulated in a dual-chamber syringe is non-inferior to the response obtained following the administration of monovalent vaccines concomitantly at two different sites. The immunogenicity was evaluated in terms of anti-HAV antibody titres reached 28 days after vaccination in initially anti-HAV seronegative subjects and in terms of anti-Vi ratio pre/post antibody titres reached 28 days after vaccination in all subjects.

  Secondary Objectives:

To compare anti-HAV and anti-Vi GMTs 28* days after vaccination.
To describe immediate and local reactions, and systemic events after vaccination.
To evaluate:

- anti-HAV and anti-Vi GMTs 14* days (D) and 1 (Y1), 2 (Y2) and 3 (Y3) years after vaccination,
- anti-HAV seroconversion rate (Ab titre rise from < 20 to ≥ 20 mIU/mL) at D14*, Y1, Y2 and Y3,
- anti-Vi seroconversion rate (four-fold rise in the pre-vaccination Ab titre) at D14*,
- anti-Vi seroprotection rate (Ab titre ≥ 1 µg/mL) at each blood sampling time (D14*, D28*, Y1, Y2 and Y3).

- Study design

  This phase 3 trial was multicentre, open, randomised and controlled in healthy subjects.

- Study population /Sample size

Sample size:

Number of subjects	Group HA/Vi	Group HA+Vi	Total
Planned to be recruited	180	180	360
Vaccinated on D0	179	181	360
Present at V4 (Year 1)	140	140	280
Present at V6 (Year 3)	112	104	216
Included in amendment #3 at V6	56	46	102
Present at V7	53	43	96

Group HA/Vi : one dose of combined HA/Vi vaccine received on D0 (V1)
Group HA+Vi: concomitant administration of monovalent HA and Vi vaccines into two different sites on D0 (V1)

Subjects included in amendment #3 received one dose of HA/Vi vaccine on Year 3.

Inclusion Criteria:
1) Age between 16 and 65 years
2) Informed consent signed by subject and by parent(s) for subjects under 18 years of age
3) Health status compatible with vaccination
4) Capable of performing self-assessment and of adhering to planned visit schedule
5) Available during the entire duration of the study

Inclusion criteria for HA/Vi injection at visit 6 (amendment #3)

1) Subject having received the combined HA/Vi vaccine or the two monovalent vaccines on D0
2) Second informed consent signed
3) Health status compatible with vaccination
4) Capable of performing self-assessment and of adhering to planned visit schedule
5) Available during the entire duration of the study
6) Negative urine pregnancy test in women of childbearing age

- Treatments

  HA/Vi combined vaccine (dual chamber presentation) – Aventis Pasteur vaccine

  Control products: Hepatitis A vaccine: AVAXIM – Aventis Pasteur vaccine
  Typhoid fever vaccine: Typhim Vi

- Outcomes/endpoints

  The *primary criterion* was the seroconversion rate for each valence:

  • for the Vi component: percentage of subjects with a four-fold increase of the anti-Vi pre-vaccination antibody titre.

  • for the HAV component: percentage of subjects for whom anti-HAV antibody titre rose from below 20 mIU/mL to 20 mIU/mL or above.

  The following parameters were measured:

  • for the Vi component: anti-Vi antibody titre before and one month after vaccination (D28 ± 4) in all subjects,

  • for the HAV component: anti-HAV antibody titre before and one month after vaccination (D28 ± 4) in seronegative subjects at inclusion (D0).

  The *secondary criteria* were:

  for the Vi component:

  • seroconversion rate, defined as the percentage of subjects with a four-fold increase of the anti-Vi pre-vaccination antibody titre (D14*).

  • seroprotection rate, defined as the percentage of subjects with a rise in anti-Vi antibody titre up to 1µg/mL or above (D14*, D28*, Y1, Y2 and Y3).

  • GMT of specific antibodies (after decimal logarithmic transformation) (D14*, D28*, Y1, Y2 and Y3).

  for the HAV component:

  • seroconversion rate, defined as the percentage of subjects with a rise in anti-HAV antibody titre from below 20 mIU/mL to 20 mIU/mL or above (D14*, Y1, Y2 and Y3).

  • GMT of specific antibodies (after decimal logarithmic transformation) (D14*, D28*, Y1, Y2 and Y3).

  The safety was evaluated in terms of the percentage of subjects with at least one immediate, local or systemic reaction.

- Statistical Methods

  Sample size was limited by the number of included subjects who attended visit on Y3. Amendment #3 was proposed to all subjects participating to Y3 visit in Netherlands.
  For this reason, it was interesting to simulate some sample size with different powers. Sample size had been calculated with the software Nquery Advisor v4.0.
  A significant level, alpha, of 2.5%, a clinically relevant difference of 1/4 in terms of GMT ratio for anti-HAV (0.602 in terms of log10 of GMT ratio) and of 1/2 in terms of GMT ratio for anti-Vi were considered.
  Furthermore, assuming that the mean and standard deviation are the same for the two groups, the sample size for each non-inferiority test and for the global test was calculated.

➢ Results

- Recruitment/ Number analysed

  Of the 360 subjects enrolled and vaccinated, a total of 280 healthy adult volunteers (140 in each group) attended visit on year 1 between 24 June 1999 and 17 April 2000. Among these subjects, 154 (81 in group HA/Vi and 73 in group HA+Vi) attended visit 6 (Year 3) in Netherlands and 102 agreed to receive a single injection of the combined HA/Vi vaccine instead of the injection of the two monovalent vaccines.

- Baseline data

Reference is made to the final report dated 3rd September 1999. No such report is included in the submission

- Efficacy results

  After statistical analysis of the first study results (final report date 3 September 1999, this was not provided along with the submission), the combined typhoid fever and hepatitis A (HA/Vi) vaccine has proved to induce a non-inferior immune response when used instead of the reference vaccines concomitantly injected into two different sites.

- Safety results

  A total of 13 SAEs were reported by 12 subjects between V3 and V6: 7 subjects in group HA/Vi experienced 8 SAEs and 5 subjects in group HA+Vi experienced 5 SAEs.
  Among these 13 SAEs, 2 were reported to the Health Authorities, one (Group HA/Vi) was considered to be related to the vaccination by the investigator and one (Group HA+Vi) was a vaccine failure to the control vaccine (Typhim Vi).

  Immediate Reactions Within 30 Minutes of HA/Vi Injection on Y3

  No immediate local and systemic reactions were observed after the injection of the HA/Vi vaccine on Y3.
  One subject (#001-00098) in group HA+Vi experienced mild asthenia within 30 minutes following HA/Vi injection. This event was not related to vaccination and disappeared within 24 hours.

  Local Reactions Within 7 Days of HA/Vi Injection on Year 3

  A total of 39 subjects (73.6%) in group HA/Vi and 30 subjects (69.8%) in group HA+Vi experienced at least one local reaction within 7 days of injection. The local safety profile was similar in both groups. Pain was the most frequently reported local reaction, usually associated with another local reaction (essentially induration/oedema). All reported local reactions occurred within 3 days following the HA/Vi injection and were of mild and moderate intensity, except 3 cases of induration/oedema which were severe.

  Local Reaction Occurring More than 7 Days After the HA/Vi Injection on Y3

  No local reaction occurred more than 7 days after HA/Vi injection

  Systemic Events Occurring Within 7 Days of HA/Vi Injection on Y3

  Systemic safety analysis within 7 days of combined vaccines injection was performed on a total of 96 subjects, 53 in group HA/Vi and 43 in group HA+Vi. A total of 16 subjects (30.2%) in group HA/Vi and 15 subjects (34.9%) in group HA+Vi experienced at least one systemic event, within 7 days of injection. A total of 16 subjects (30.2%) in group HA/Vi and 13 subjects (30.2%) in group HA+Vi experienced at least one systemic reaction (i.e., *related to vaccination*) within 7 days of injection.

  The systemic safety profile was similar in both groups, myalgia was the most commonly reported systemic reaction (10 cases in group HA/Vi and 9 cases in group HA+Vi). All reactions were judged possibly related to vaccination, except one case: subject #001-00152 (group HA/Vi) experienced a mild myalgia definitely related to vaccination lasting less than four days.

  Systemic Events Occurring More Than 7 Days After HA/Vi Injection on Y3

  Four systemic events were reported more than 7 days after the HA/Vi injection. Among these events 3 were possibly related to vaccination by the investigator (2 in group HA/Vi and 1 in group HA+Vi).

Assessor's/Rapporteur´s comment:

The study report provided does not allow drawing specific conclusions with regards to the paediatric population, since only one subject aged 17 years was included in the trial (001-00024).

*Study 15 - (**CYD05**): "Safety of ChimeriVax™Dengue Tetravalent Vaccine in Subjects Aged 2 to 45 Years in the Philippines"*

The trial period was from 2006 - 2007

- **Description**

The present trial was set up to evaluate the safety of a tetravalent formulation (~5 log10 CCID50 per serotype) given in a two-dose primary schedule (3 to 4 months apart) and a third dose at one year after the first vaccination in subjects aged 2 to 45 years in the Philippines. For the safety assessment of the tetravalent formulation at the first injection, a control group received a registered vaccine (Typhim VI).
As a safety precaution, this trial used a stepwise approach: adults (18 to 45 years) were vaccinated first, then adolescents (12 to 17 years), then children aged 6 to 11 years, and finally children aged 2 to 5 years.

- **Methods**

  - Objective(s)

    1) To describe the safety of each injection of ChimeriVax™ dengue tetravalent vaccine in four age groups of subjects: adults (18 to 45), adolescents (12 to 17), children (6 to 11), and children (2 to 5).

    2) To describe viremia after each injection of ChimeriVax™ dengue tetravalent vaccine in the four age groups of subjects.

    3) To describe the humoral immune response against dengue before injection, and after each injection of ChimeriVax™ dengue tetravalent vaccine in the four age groups of subjects.

    4) To evaluate the persistence of antibodies against dengue during the four years after the last injection of ChimeriVax™ dengue tetravalent vaccine in the four age groups of subjects.

    Observational Objectives

    1) To explore whether there was a correlation between a Human Leukocyte Antigen (HLA) type and the response to ChimeriVax™ dengue tetravalent vaccine (in terms of reactogenicity and nature of immune response) in the four age groups of subjects.
    2) To describe the phenotypic and genetic stability of ChimeriVax™ dengue viruses isolated from the vaccinated viremic subjects.
    3) To describe the immune response against typhoid before and after the first injection of a control vaccine (Typhim Vi).
    4) To describe the serological status for Japanese encephalitis (JE) in the study population at baseline
    5) To detect symptomatic dengue cases throughout the four years after the last study injection.

- Study design

  This was a blind observer (first injection), open (second and third injections), monocenter, randomized, controlled, Phase I study in 126 subjects in the Philippines (18 adults, 36 adolescents aged 12 to 17 years, 36 children aged 6 to 11 years, and 36 children aged 2 to 5 years).
  Enrolment was sequential and based on a stepwise approach.
  For each age cohort, subjects were randomly assigned to one of the two groups: Group 1 (dengue vaccine) and Group 2 (Control Group, Typhim Vi). Three injections were given on D0, D0 + 105 days, and D0 + 365 days.

  Group 1 received the live-attenuated dengue vaccine (serotypes 1, 2, 3, and 4) as first, second and third injections.

  Group 2 (Control Group) received Typhim Vi as first injection and dengue vaccine (serotypes 1, 2, 3, and 4) as second and third injections.

  Blood samples were drawn in all study subjects in the 28 days following each vaccination to assess immunogenicity.

- Study population /Sample size

  Inclusion Criteria:
  A potential subject had to meet all of the following criteria to be considered for trial enrolment:

  1) Aged 2 to 45 years on the day of inclusion (Scr.)
  2) Informed consent form signed by the subject, by an independent witness, and by the parent(s) or another legal representative for subjects under 18 years old (Scr.)
  3) For a woman, inability to bear a child or negative serum pregnancy test at screening (Scr.)
  4) Able to attend all scheduled visits and to comply with all trial procedures (Scr.+V01)
  5) For a woman of child-bearing potential, use of an effective method of contraception or abstinence for at least four weeks prior to the first vaccination and at least four weeks after each vaccination (Scr.+V01)
  6) For a woman, inability to bear a child or negative urine pregnancy test on the day of the first injection (V01)

  A sufficient number of healthy subjects was screened from either volunteer subjects or in response to study advertisement, such that 18 male or female volunteers aged 18 to 45, 36 adolescent volunteers aged 12 to 17, 36 children aged 6 to 11, and 36 children aged 2 to 5 were actually randomized. Adult subjects were included first, then adolescents, then children from 6 to 11 years, and children from 2 to 5 years.

- Treatments

  Investigational Product: ChimeriVax™ Dengue Tetravalent Vaccine

  Control Product: Typhim Vi

- Outcomes/endpoints

  The primary endpoints for the safety evaluation were:
  • The occurrence, time to onset, number of days of occurrence, severity, and action taken of the following solicited (i.e., items prelisted in the subject's diary card and Case Report Form, CRF) injection site reactions occurring between D0 and D7 after each injection:
  • The occurrence, time to onset, number of days of occurrence, severity, and action taken of the following solicited systemic reactions between D0 and D14 after each injection:

• The occurrence, nature (MedDRA [Medical Dictionary for Regulatory Activities] preferred term), time to onset, duration, severity, action taken, and relationship to vaccination of unsolicited (i.e., spontaneously reported) AEs (injection site and systemic) between D0 and the following visit (D28±2 days) after each injection.
• SAEs throughout the trial.
• Occurrence and timing of out-of-normal-range biological test results up to 28 days after each injection.

- Statistical Methods

  The analysis was descriptive and presented by group with 95% Confidence Intervals (CIs) for main parameters. Listings of uncleaned safety data were performed by Data Management after each age cohort had completed Day 14 visit (including viremia data). These data were provided by the Sponsor to the IDMC. The main listings included in this analysis were defined in agreement with the members of the IDMC. Two interim statistical analyses of safety, viremia, and immunogenicity were performed on unblinded Day 28 data of the first and second injections in the whole study population.

➢ Results

- Recruitment/ Number analysed

  A total of 191 subjects were screened. All of them were eligible for inclusion in the study. A total of 126 subjects were randomized (18 adults, 36 adolescents, 36 children aged 6 to 11 years and 36 children aged 2 to 5 years).
  First Vaccination (V01): 126 subjects (100.0%) received a subcutaneous injection in the deltoid area of either dengue vaccine [84 subjects (100%)] or typhoid vaccine [42 subjects (100%).
  Second Vaccination (V06): 121 subjects (96.0%) (82 subjects [97.6%] in Group 1 and 39 subjects [92.9%] in Group 2) were present at V06. None had a definitive contra-indication and all received a subcutaneous injection in the deltoid area of the left arm of dengue vaccine.
  Third Vaccination (V11): 119 subjects (94.4%) (80 subjects [95.2%] in Group 1 and 39 subjects [92.9%] in Group 2) were present at V11. None had a definitive contra-indication and all received a subcutaneous injection in the deltoid area of dengue vaccine.

- Baseline data

  The mean age (±SD) was 12.2 years (± 8.3) in Group 1: 27.7 years (± 8.3) in adults, 15.2 years (± 1.7) in adolescents, 9.4 years (± 1.8) in children 6 to 11 years, and 4.3 years (± 1.1) in children 2 to 5 years).
  In Group 2 the mean age was 12.2 years (± 9.5): 30.8 years (± 10.5) in adults, 14.5 years (± 1.9) in adolescents, 9.1 years (±1.5) in children (6 to 11 years), and 3.7 years (±0.7) in children (2 to 5 years).
  In Group 1, distribution of female/male by age was similar overall and by age groups (about half of them were either females or males), while in Group 2 the proportion of female was higher than male subjects in all age groups except in children (6 to 11 years).

Table 9.1: Subjects Included per Age Group (All Screened Subjects)

	ChimeriVax™ n(%)	Typhim Vi® n(%)	All Randomized n(%)	Not Randomized n(%)	All n(%)
N screened*	84 (100.0)	42 (100.0)	126 (100.0)	65 (100.0)	191 (100.0)
Adults [18-45] years	12 (14.3)	6 (14.3)	18 (14.3)	6 (9.2)	24 (12.6)
Adolescents [12-17] years	24 (28.6)	12 (28.6)	36 (28.6)	18 (27.7)	54 (28.3)
Children [6-11] years	24 (28.6)	12 (28.6)	36 (28.6)	15 (23.1)	51 (26.7)
Children [2-5] years	24 (28.6)	12 (28.6)	36 (28.6)	26 (40.0)	62 (32.5)

- Efficacy results

  There were no primary objectives for efficacy.

- Safety results

  During the study, 2 subjects in Group 2 experienced one SAE each after the second vaccination(first dose of dengue vaccine). One subject experienced two episodes of dyspepsia, and the second episode was associated with upper respiratory tract infection. The other subject developed urinary tract infection. These SAEs were considered as not related to the study vaccine by the Investigator, the Sponsor and the IDMC. Both subjects recovered and continued the study. No SAEs were reported after the first or third vaccination.

  After the first study vaccination, injection site reactions were markedly more frequent (83.3% versus 29.8%) in the Typhim Vi vaccine recipients (Group 2) than in subjects receiving the dengue vaccine (Group 1).

  After the second vaccination, systemic reactions and injection site reactions were slightly higher in Group 2 (first dose of dengue vaccine) than in Group 1 (second dose of dengue vaccine).

  After the first vaccination, there was no difference in the proportion of subjects experiencing systemic reactions between Group 1 (dengue vaccine) and Group 1 (Typhim Vi).

  Unsolicited AEs were reported in 48.8% of subjects in Group 1 and 54.8% in Group 2 after the first vaccination. These proportions were stable after the second and third vaccinations with respectively 51.2% and 48.8% in Group 1 and 61.5% and 53.8% in Group 2. The most frequently reported unsolicited AEs were upper respiratory tract infection, nasopharyngitis and biological abnormalities in the two groups. Intercurrent infections were more frequent in children, especially after the first vaccination.

  The proportion of systemic reactions was slightly higher in Group 1 (60.7%) than in Group 2 (48.7%), while the proportion of injection site reactions was similar in the two groups, 29.8% and 25.6%, respectively. When safety results were classified by

  age groups, injection site and systemic reactogenicity was not increased in the younger population compared to adults or adolescents. In terms of severity, one severe systemic reaction (fever) was reported in children (aged 2 to 5 years) receiving the first dose of dengue vaccine in Group 2 (possibly due to concomitant acute bronchitis). No severe injection site reactions occurred after the first dose of dengue vaccine.

  More injection site reactions were observed in Group 2 (83.3%) than in Group 1 (29.8%) after the first vaccination (Typhim Vi vaccination vs dengue vaccine vaccination). Pain was the most frequent injection site reaction after one, two, or three vaccinations followed by erythema and edema. The proportion of subjects who reported at least one episode of pain within the 7 days after the first vaccination was: 21 subjects (25.0%) in Group 1 who received the dengue vaccine and 28 subjects (66.7%) in Group 2 after Typhim Vi vaccination.

  Headache was the most frequently reported solicited systemic reaction after each vaccination,followed by malaise, myalgia, fever and asthenia. The proportions of subjects reporting headache were 35.7%, 28.0%, and 17.5% in Group 1 after the first, second and third doses of dengue vaccine respectively, and 23.8% (after Typhim Vi vaccination), 25.6%, and 20.5% in Group 2 after the first and second doses of dengue vaccine, respectively. „Objective adverse reactions „as pyrexia were more frequently observed in children (as a possible result of intercurrent infections), and “subjective adverse reactions” were more frequent in adults (headache and myalgia) or in adolescents (asthenia and malaise).

  Solicited fever was more frequent after the first vaccination in subjects in Group 1 (20 subjects, 23.8%) receiving dengue vaccine than in subjects in Group 2 (3 subject, 7.1%) receiving Typhim Vi.

In the two groups, episodes of systemic reactions occurred mainly between Day 0 and Day 3 after each vaccination (until Day 7 for fever), and were present for a maximum of 3 days. Most episodes were mild or moderate and resolved spontaneously.
A limited number of biological abnormalities were rated as severe: one subject in Group 2 (one increase in CPK after the first vaccination with Typhim Vi), one child in Group 1 with an increase of AST/ALT at the pre-vaccination 2 visit (that was given with a two week delay), one adult in Group 1 after the second dose of dengue vaccine (increase in CPK related to physical activity) and one 2 to 5-year-old child in Group 1 after the third dose of dengue vaccine (increase in CPK, concomitant with a detected vaccinal viremia but without any clinical sign of reactogenicity or any other biological abnormalities). In adult and adolescent groups the viremia were detected mainly after the first administration of the vaccine.
Adults presented higher antibody levels at baseline and reached a 100% success rate with the four serotypes after the first dose of dengue vaccine. A total of 66% of the 2 to 5-year-old children were flavivirus immune at baseline and this age group reached 100% success rate with the four serotypes after completion of the different dengue vaccination schedules applied in Group 1 and in Group 2. In adolescents with 97.2% of flavivirus immune subjects at baseline, the success rates with the four serotypes were 83.3% and 90.9% for Group 1 and Group 2, respectively, while in 6 to 11-year-old children with 66.6% of flavivirus immune subjects at baseline, the success rates with the four serotypes reached 79.2% for Group 1 and 63.6% for Group 2.

Overall, viremia was very low, under the lower limit of quantitation of the different assays involved in measurement. This observation corroborates the good safety profile of the vaccine.

Assessor's/Rapporteur´s comment:

It has to be noted that Typhim Vi however was not the vaccine of primary interest per se since purpose of this study was to evaluate the safety of a ChimeriVax Dengue tetravalent formulation (with a higher virus concentration for each serotype given in several injections) as first, second and third injection (in Group 1) while a control group (Group 2) received a registered vaccine (Typhim VI) as first injection and dengue vaccine as second and third. Safety results can be therefore only be extrapolated from Group 2 after first vaccination to a rather limited extend considering the small sample size of the paediatric subset (Group 2 n after first vaccination with Typhim consisted of 12 adolescents aged 12 to 17, 12 Children aged 6 to 11, 12 children aged 2 to 5 and 6 adults aged 18 to 45).

When looking at the safety summary of the First Vaccination, remarkably, the injection site reactions and pain seem to have occurred more frequently in the control group after vaccination with Typhim Vi.

Table 5.1: Safety Summary on First, Second and Third Vaccination Periods

	First Vaccination				Second Vaccination				Third Vaccination			
	Group 1: CYD TV (N=84)		Group 2: TYV (N=42)		Group 1: CYD TV → CYD TV (N=82)		Group 2: TYV→ CYD TV (N=39)		Group 1: CYD TV → CYD TV → CYD TV (N=80)		Group 2: TYV→ CYD TV → CYD TV (N=39)	
	n	%	n	%	n	%	n	%	n	%	n	%
Subjects with at least one:												
- Clinically significant biological abnormality*	13	15.5	7	16.7	14	17.1	6	15.4	15	18.8	6	15.4
- Event	67	79.8	40	95.2	54	65.9	31	79.5	56	70.0	29	74.4
- Reaction	55	65.5	39	92.9	39	47.6	21	53.8	30	37.5	16	41.0
- Injection site reaction	25	29.8	35	83.3	16	19.5	10	25.6	14	17.5	12	30.8
- Systemic reaction	51	60.7	22	52.4	32	39.0	19	48.7	26	32.5	10	25.6
- Severe event	1	1.2	1	2.4	3	3.7	1	2.6	1	1.3	0	0.0
- Severe reaction	0	0.0	1	2.4	3	3.7	1	2.6	0	0.0	0	0.0
- Severe injection site reaction	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Severe systemic reaction	0	0.0	1	2.4	3	3.7	1	2.6	0	0.0	0	0.0
- SAE (within 28 days after vaccination)	0	0.0	0	0.0	0	0.0	1	2.6	0	0.0	0	0.0
SAE leading to withdrawal	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

* As judged by the Investigator in the CRF
N=Number of subjects; n(%)=number and percentage of subjects presenting events
CYD: dengue vaccine as first, second and third injections. TYV: Typhim Vi® as first injection
(Source: Section 9, Table 9.154, Table 9.178 and Table 9.202).

Table 5.2: Number and Percentage of Subjects With Solicited Reactions – First, Second and Third Vaccination Periods

	First Vaccination				Second Vaccination				Third Vaccination			
	Group 1: CYD TV (N=84)		Group 2: TYV (N=42)		Group 1: CYD TV →CYD TV (N=82)		Group 2: TYV→ CYD TV (N=39)		Group 1: CYD TV → CYD TV → CYD TV (N=80)		Group 2: TYV → CYD TV → CYD TV (N=39)	
	n	%	n	%	n	%	n	%	n	%	n	%
SOLICITED INJECTION SITE REACTIONS												
Injection site pain	21	25.0	28	66.7	15	18.3	10	25.6	11	13.8	10	25.6
Injection site erythema	7	8.3	16	38.1	5	6.1	1	2.6	3	3.8	4	10.3
Injection site edema	3	3.6	16	38.1	2	2.4	2	5.1	0	0.0	5	12.8
SOLICITED SYSTEMIC REACTIONS												
Fever	20	23.8	3	7.1	10	12.2	13	33.3	9	11.3	4	10.3
Headache	30	35.7	10	23.8	23	28.0	10	25.6	14	17.5	8	20.5
Malaise	19	22.6	7	16.7	18	22.0	9	23.1	10	12.5	1	2.6
Myalgia	16	19.0	7	16.7	12	14.6	3	7.7	9	11.3	1	2.6
Asthenia	17	20.2	6	14.3	11	13.4	6	15.4	6	7.5	2	5.1

N=Number of subjects
n(%)=number of subjects presenting events
CYD TV: dengue vaccine as first, second and third injections. TYV: Typhim Vi® as first injection and dengue vaccine second and third injections
(Source: Section 9, Table 9.161, Table 9.166, Table 9.190, Table 9.209, Table 9.214)

When safety results were classified by age groups, most reactions occurred in adults and adolescents.

However, as already mentioned above, considering the small sample size of paediatric subjects (12 to 17 n= 12; 6 to 11 n= 12; 2 to 5 n=12) this study, the interpretation of the study results with regards to this subset is considered rather to be of limited extend.

- **Pooled Analysis**

The applicant has furthermore provided an analysis across the trials summarized above by pooling of the results. The results are summarized below:

The assessment of the safety profile of Typhim Vi vaccine was an objective of each of the 6 Sanofi Pasteur-sponsored studies. The safety of Typhim Vi vaccine was evaluated for at least 7 days after 1 injection in subjects 2 years of age and above. Typhim Vi vaccine was the investigational product in 1 study (Study 30, TYP31), and for the remaining 5 studies, Typhim Vi vaccine was a control vaccine.

All studies had subjects who were ≥ 18 years of age and 3 studies had subjects who were 2 to 17 years of age: Study 12 (AVI01398), Study 15 (CYD05), Study 29 (CYD22), and Study 30 (TYP31).

The pooled analysis included subgroups by age and by injection with a concomitant vaccine. Age subgroups were calculated according to the age at the time of the Typhim Vi vaccine injection and were grouped as follows:

- 2 to 11 years (child subgroup)
- 12 to 17 years (adolescent subgroup)
- < 18 years (paediatric subgroup)
- ≥ 18 years (adult subgroup)

The adult pooled safety analysis is used as reference and is included for comparison.

The "per injection with a concomitant vaccine subgroup" was comprised of 2 main groups: subjects who received Typhim Vi vaccine alone, and those subjects whom had received Typhim Vi vaccine concomitantly with another vaccine. Subjects received a concomitant vaccine with Typhim Vi vaccine in 3 studies: Study 11 (YF18901), (AVI01398), and Study 14 (MTA11).

The per injection with a concomitant vaccine subgroup had 2 categories:

"With Concomitant Vaccinea":

- Subjects from Group B in Study 11 (YF18901)
- Subjects from Group B in Study 12 (AVI01398)
- Subjects from Group A and B in Study 14 (MTA11)

"Without Concomitant Vaccinea":

- Subjects from Group D in Study 11 (YF18901)
- Subjects from Study 15 (CYD05) who received Typhim Vi vaccine
- Subjects from control group in Study 29 (CYD22) who received Typhim Vi vaccine as third vaccination
- All subjects from Study 30 (TYP31)

- Safety Endpoints

For the pooled safety analysis, AEs were calculated for the solicited period, defined as the 7-day period following vaccination, for both injection site reactions and systemic reactions in all studies.

The following *solicited reactions* within 7 days after vaccination were evaluated:

- Solicited injection site reactions: pain, erythema (erythema/redness combined), swelling (edema/swelling/induration combined), and ecchymosis,
- Solicited systemic reactions: fever, fatigue (asthenia/fatigue), headache, malaise, myalgia, and chill.

Unsolicited non-serious adverse reactions ([ARs], i.e., AEs related to study vaccine) were assessed during the 28-day period following vaccination.

In the studies in which a concomitant vaccine was received, unsolicited injection site AEs related to the Typhim Vi vaccine were identified as those that occurred on the side where the Typhim Vi vaccine was administered to the subject. Therefore, only the 2 studies below were considered for unsolicited injection site AEs:

- Unsolicited injection site reactions at Typhim Vi injection side of subjects from group B in Study 12 (AVI01398)
- Unsolicited injection site reactions at Typhim Vi injection side of subjects from Study 14 (MTA11)

While unsolicited injection site reactions could be determined by the side of the injection on the subject, the unsolicited systemic reactions could not be particularly linked to 1 of the 2 vaccines received. Therefore, the following subjects were excluded of the analysis of unsolicited systemic reactions in the analyses of all subgroups and by age group; however, these subjects were included in the analyses of the Per Injection with a concomitant vaccine subgroup.

- All subjects from Study 12 (AVI01398)
- All subjects from Study 14 (MTA11)

The occurrence of related Adverse Events of Special Interest (AESIs) within 28 days following vaccine injection was assessed. AESIs included anaphylaxis, serum sickness, and vasovagal syncope.

- Study population /Sample size

Data from 1532 subjects who received at least 1 injection of Typhim Vi vaccine were included in the analysis. The mean age of the subjects was 30.5 years (ranging from 2 years to 64 years of age). There were more female subjects (59.3%) than male subjects (40.7%). Most subjects (93.7%) were ≥ 18 years of age, 6.3% of subjects were < 18 years of age, 4.4% were 2 to 11 years of age and 2.0% were 12 to 17 years of age.

The mean age was 6.6 years for subjects 2 to 11 years of age, 14.3 years for subjects 12 to 17 years of age, 9.0 years for subjects < 18 years of age, and 32.0 years for subjects ≥ 18 years of age.

Of the 1532 subjects, 352 (23.0%) subjects received Typhim Vi vaccine alone and 1180 (77.0%) subjects received Typhim Vi vaccine with a concomitant vaccine (YF vaccine, HA, TetraMenD, or placebo.

- Safety Results

A total of 1435 adults and 97 adolescents and children are included in the analysis. In this section primarily the results which were listed by age group are summarized (and not the complete pooled results of adults, adolescents and children together), in order to gain an overview of solicited and unsolicited reactions by age group, especially considering the fact, that in the course of the paediatric work-sharing procedure, the paediatric subset id the primary focus. Some Aspects of the complete pooled results is given in the Assessor's overall conclusion on the pooled analysis.

Solicited Reactions within 7 Days After Vaccine Injection - Safety Analysis Set by Age Group

The age subgroups include the child subgroup (2 to 11 years of age), the adolescent subgroup (subjects 12 to 17 years of age), all paediatric subjects (< 18 years of age) and adult subjects (≥ 18 years of age).

Table 7: Summary of solicited reactions within 7 days by age group - SafAS

	Child 2 to 11 years (N=67)			Adolescent 12 to 17 years (N=30)			All Pediatric Subjects < 18 years (N=97)			Adult Subjects ≥ 18 years (N=1435)		
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Solicited reaction	38/67	56.7	(44.0; 68.8)	25/30	83.3	(65.3; 94.4)	63/97	64.9	(54.6; 74.4)	1098/1413	77.7	(75.4; 79.9)
Grade 3 solicited reaction	1/67	1.5	(0.0; 8.0)	0/30	0.0	(0.0; 11.6)	1/97	1.0	(0.0; 5.6)	20/1413	1.4	(0.9; 2.2)
Solicited injection site reaction	35/67	52.2	(39.7; 64.6)	23/30	76.7	(57.7; 90.1)	58/97	59.8	(49.3; 69.6)	1083/1413	76.6	(74.3; 78.8)
Grade 3 injection site reaction	0/67	0.0	(0.0; 5.4)	0/30	0.0	(0.0; 11.6)	0/97	0.0	(0.0; 3.7)	16/1413	1.1	(0.6; 1.8)
Solicited systemic reaction	15/67	22.4	(13.1; 34.2)	11/29	37.9	(20.7; 57.7)	26/96	27.1	(18.5; 37.1)	117/256	45.7	(39.5; 52.0)
Grade 3 systemic reaction	1/67	1.5	(0.0; 8.0)	0/29	0.0	(0.0; 11.9)	1/96	1.0	(0.0; 5.7)	4/256	1.6	(0.4; 4.0)

Source: Appendix 3, Table 1.18
n: number of subjects experiencing the endpoint listed in the first column
M: number of subjects with available data for the relevant endpoint
CI: confidence interval
The following solicited systemic reactions are excluded: Chills from Study 11(YF18901)
Solicited systemic ARs from Groups B of Study 11 (YF18901), Study 12 (AVI01398) and Study 14 (MTA11) are excluded
Only solicited injection site reactions occurred at the side of Typhim vaccination are considered

Table 8: Solicited reactions within 7 days after vaccine injection by age group - SafAS

	Child 2 to 11 years (N=67)			Adolescent 12 to 17 years (N=30)		
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Solicited reaction	38/67	56.7	(44.0; 68.8)	25/30	83.3	(65.3; 94.4)
Injection site reaction	35/67	52.2	(39.7; 64.6)	23/30	76.7	(57.7; 90.1)
Injection site pain	28/67	41.8	(29.8; 54.5)	23/30	76.7	(57.7; 90.1)
Injection site erythema*	14/67	20.9	(11.9; 32.6)	0/30	0.0	(0.0; 11.6)
Injection site swelling†	15/67	22.4	(13.1; 34.2)	1/30	3.3	(0.1; 17.2)
Injection site ecchymosis	0/0	NA	NA	0/1	0.0	(0.0; 97.5)
Systemic reaction	15/67	22.4	(13.1; 34.2)	11/29	37.9	(20.7; 57.7)
Fever	1/67	1.5	(0.0; 8.0)	0/29	0.0	(0.0; 11.9)
Asthenia/Fatigue	1/62	1.6	(0.0; 8.7)	3/22	13.6	(2.9; 34.9)
Headache	8/67	11.9	(5.3; 22.2)	5/29	17.2	(5.8; 35.8)
Malaise	3/67	4.5	(0.9; 12.5)	3/29	10.3	(2.2; 27.4)
Myalgia	6/67	9.0	(3.4; 18.5)	8/29	27.6	(12.7; 47.2)
Chills	0/0	NA	NA	0/0	NA	NA
	All Pediatric Subjects < 18 years (N=97)			**Adult Subjects ≥ 18 years (N=1435)**		
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Solicited reaction	63/97	64.9	(54.6; 74.4)	1098/1413	77.7	(75.4; 79.9)
Injection site reaction	58/97	59.8	(49.3; 69.6)	1083/1413	76.6	(74.3; 78.8)
Injection site pain	51/97	52.6	(42.2; 62.8)	1068/1413	75.6	(73.3; 77.8)
Injection site erythema*	14/97	14.4	(8.1; 23.0)	109/1412	7.7	(6.4; 9.2)
Injection site swelling†	16/97	16.5	(9.7; 25.4)	84/1411	6.0	(4.8; 7.3)
Injection site ecchymosis	0/1	0.0	(0.0; 97.5)	2/178	1.1	(0.1; 4.0)
Systemic reaction	26/96	27.1	(18.5; 37.1)	117/256	45.7	(39.5; 52.0)
Fever	1/96	1.0	(0.0; 5.7)	0/256	0.0	(0.0; 1.4)
Asthenia/Fatigue	4/84	4.8	(1.3; 11.7)	4/16	25.0	(7.3; 52.4)
Headache	13/96	13.5	(7.4; 22.0)	16/204	7.8	(4.5; 12.4)
Malaise	6/96	6.3	(2.3; 13.1)	34/256	13.3	(9.4; 18.1)
Myalgia	14/96	14.6	(8.2; 23.3)	96/204	47.1	(40.1; 54.2)
Chills	0/0	NA	NA	0/51	0.0	(0.0; 7.0)

Source: Appendix 3, Table 1.19

NA: Not Applicable

n: number of subjects experiencing the endpoint listed in the first column

M: number of subjects with available data for the relevant endpoint

CI: confidence interval

Solicited systemic ARs from Groups B of Study 11 (YF18901), Study 12 (AVI01398) and Study 14 (MTA11) are excluded

Only solicited injection site reactions occurred at the side of Typhim vaccination are considered

* Includes redness

† Includes injection site edema/swelling/induration

Assessor's/Rapporteur´s comment:

In each of the age subgroups, most or all of the solicited reactions were of Grade 1 or 2 severities.

In the child and adolescent subgroups, the percentage subjects experiencing at least 1 solicited systemic reaction within 7 days after vaccine injection was 22.4% and 37.9%, respectively. In the subgroups of all paediatric subjects and adult subjects, the percentage of subjects experiencing at least 1 solicited systemic reaction within 7 days after vaccine injection was 27.1% and 45.7%, respectively.
The most common solicited reaction in the child and adolescent subgroup were obviously local reactions, such as injection site pain (41.8% in the child subgroup and 76.7% in the adolescent subgroup). Furthermore, injection site swelling and injection site erythema were frequently reported (22.4% in the child subgroup and 20.9% in the adolescent subgroup).
In the child subgroup (2 to 11 years of age), headache was the most frequently reported solicited systemic reaction (11.9%, 8/67 subjects). In the adolescent subgroup (12 to 17 years of age), myalgia was the most frequently reported (≥ 10%) solicited systemic reaction (27.6%, 8/29 subjects), followed by headache (17.2%), asthenia/fatigue (13.6%), and malaise (10.3%).

When comparing the all paediatric subgroup and the adult subjects the most frequently reported injection site reaction was injection site pain (experienced in 52.6% of subjects and 75.6% for subjects, respectively). In the all paediatric subgroup, injection site swelling (16.5%) and injection site erythema (14.4%) were frequently reported. In the subgroup of all paediatric subjects, myalgia was the most frequently reported solicited systemic reaction (14.6%), followed by headache (13.5%). In the adult subgroup, myalgia was the most frequently reported solicited systemic reaction (47.1%), followed by asthenia/fatigue (25.0%), and malaise (13.3%).

The MAH´s effort to pool paediatric subjects throughout the studies in order to be able to draw conclusions on the safety profile is acknowledged, since when looking at the studies separately, the number of paediatric subjects is rather limited. However, even if the paediatric subjects are pooled, it is difficult to draw any specific conclusions on the safety profile, since the conduct of the studies showed various differences, e.g. in most of the studies Typhim was not the vaccine of primary interest and was only applied as a control vaccine or concomitantly. Nonetheless, obviously the most common solicited reaction in the child and adolescent subgroup were local reactions such as injection site pain while the most frequently reported solicited systemic reaction was headache, myalgia, asthenia/fatigue, and malaise. These AR are reflected is the MAH´s proposal for revision of section 4.8 of the SmPC and the corresponding section of the PIL.

Unsolicited Non-serious ARs within 28 Days after Vaccine Injection per Age Group

The age subgroups include the child subgroup (2 to 11 years of age), the adolescent subgroup (subjects 12 to 17 years of age), all paediatric subjects (< 18 years of age) and adult subjects (≥ 18 years of age).

Table 9: Summary of unsolicited non-serious ARs within 28 days* after vaccine injection by age group - SafAS

	Child 2 to 11 years (N=67)				Adolescent 12 to 17 years (N=30)			
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n ARs**	**n/M**	**%**	**(95% CI)**	**n ARs**
Unsolicited non-serious AR	3/67	4.5	(0.9; 12.5)	3	1/30	3.3	(0.1; 17.2)	1
Grade 3 unsolicited non-serious AR	1/67	1.5	(0.0; 8.0)	1	0/30	0.0	(0.0; 11.6)	0
Unsolicited non-serious injection site AR	0/67	0.0	(0.0; 5.4)	0	0/30	0.0	(0.0; 11.6)	0
Grade 3 unsolicited non-serious injection site AR	0/67	0.0	(0.0; 5.4)	0	0/30	0.0	(0.0; 11.6)	0
Unsolicited non-serious systemic AR	3/67	4.5	(0.9; 12.5)	3	1/30	3.3	(0.1; 17.2)	1
Grade 3 unsolicited non-serious systemic AR	1/67	1.5	(0.0; 8.0)	1	0/30	0.0	(0.0; 11.6)	0
	All Pediatric Subjects < 18 years (N=97)				**Adult Subjects ≥ 18 years (N=1329)**			
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n ARs**	**n/M**	**%**	**(95% CI)**	**n ARs**
Unsolicited non-serious AR	4/97	4.1	(1.1; 10.2)	4	4/1329	0.3	(0.1; 0.8)	4
Grade 3 unsolicited non-serious AR	1/97	1.0	(0.0; 5.6)	1	0/1329	0.0	(0.0; 0.3)	0
Unsolicited non-serious injection site AR	0/97	0.0	(0.0; 3.7)	0	4/1329	0.3	(0.1; 0.8)	4
Grade 3 unsolicited non-serious injection site AR	0/97	0.0	(0.0; 3.7)	0	0/1329	0.0	(0.0; 0.3)	0
Unsolicited non-serious systemic AR	4/97	4.1	(1.1; 10.2)	4	0/1329	0.0	(0.0; 0.3)	0
Grade 3 unsolicited non-serious systemic AR	1/97	1.0	(0.0; 5.6)	1	0/1329	0.0	(0.0; 0.3)	0

Source: Appendix 3, Table 1.20

n: number of subjects experiencing the endpoint listed in the first column

CI: confidence interval

n ARs: number of ARs

Study 11(YF18901) is excluded from analysis of unsolicited AR

Unsolicited systemic ARs from Study 12 (AVI01398) and Study 14 (MTA11) are excluded

Only unsolicited injection site reactions occurred at the side of Typhim vaccination are considered

*27 days after injection in Study 14 (MTA11)

Table 10: Unsolicited non-serious ARs within 28 days after vaccine injection by age group and by system organ class and preferred term - SafAS

	Child 2 to 11 years (N=67)				Adolescent 12 to 17 years (N=30)			
Subjects experiencing at least one:	**n**	**%**	**(95% CI)**	**n ARs**	**n**	**%**	**(95% CI)**	**n ARs**
Unsolicited non-serious AR*	3	4.5	(0.9; 12.5)	3	1	3.3	(0.1; 17.2)	1
Investigations	3	4.5	(0.9; 12.5)	3	1	3.3	(0.1; 17.2)	1
Blood creatinine phosphokinase increased	2	3.0	(0.4; 10.4)	2	1	3.3	(0.1; 17.2)	1
Alanine aminotransferase increased	1	1.5	(0.0; 8.0)	1	0	0.0	(0.0; 11.6)	0
	All Pediatric Subjects < 18 years (N=97)				**Adult Subjects ≥ 18 years (N=1435)**			
Subjects experiencing at least one:	**n**	**%**	**(95% CI)**	**n ARs**	**n**	**%**	**(95% CI)**	**n ARs**
Unsolicited non-serious AR*	4	4.1	(1.1; 10.2)	4	4	0.3	(0.1; 0.7)	4
Investigations	4	4.1	(1.1; 10.2)	4	0	0.0	(0.0; 0.3)	0
Blood creatinine phosphokinase increased†	3	3.1	(0.6; 8.8)	3	0	0.0	(0.0; 0.3)	0
Alanine aminotransferase increased†	1	1.0	(0.0; 5.6)	1	0	0.0	(0.0; 0.3)	0
General disorders and administration site conditions	0	0.0	(0.0; 3.7)	0	3	0.2	(0.0; 0.6)	3
Injection site pruritus	0	0.0	(0.0; 3.7)	0	2	0.1	(0.0; 0.5)	2
Feeling hot	0	0.0	(0.0; 3.7)	0	1	< 0.1	(0.0; 0.4)	1
Musculoskeletal and connective tissue disorders	0	0.0	(0.0; 3.7)	0	1	< 0.1	(0.0; 0.4)	1
Musculoskeletal stiffness	0	0.0	(0.0; 3.7)	0	1	< 0.1	(0.0; 0.4)	1

Source: Appendix 3, Table 1.21

n: number of subjects experiencing the endpoint listed in the first column

CI: confidence interval

n ARs: number of ARs

Unsolicited systemic ARs from Study 12 (AVI01398) and Study 14 (MTA11) are excluded

Only unsolicited injection site reactions occurred at the side of Typhim vaccination are considered

*27 days after injection in Study 14 (MTA11)

† ARs that were clinically significant abnormal values from biological safety tests (biochemistry and hematology) that were specifically performed during Study 15 (CYD05) and Study 29 (CYD22) and were reported by the investigator as unsolicited ARs.

Assessor's/Rapporteur´s comment:

The unsolicited ARs in the 4 subjects in the paediatric subgroup were biological safety investigations from Study 15 (CYD05) and Study 29 (CYD22), which as previously noted, are not a focus of the pooled analysis.
In the adult subgroup, at least 1 unsolicited non-serious AR within 28 days after vaccine injection was experienced by 0.3% (4/1426) of subjects and no Grade 3 ARs were reported.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

➢ Overall conclusion

Based on the studies submitted by the applicant, the Rapporteur concludes that the benefit risk ratio of Salmonella Typhimurium has not changed for the licensed product Typhim Vi vaccine in children and adolescents.

The Applicant has proposed changes in section 4.8 of the SmPC which are based on the results obtained in the paediatric subset of subjects.

Several studies do have their limitation regarding specific information to be obtained for the paediatric population, such as the fact, that only a small to a very small number has been included in the studies, which might mask small differences in safety signals. Furthermore, Typhim Vi was not the vaccine of primary interest in most of the studies, but was only applied as vaccine in the control group or concomitantly with other vaccination. Therefore caution is required when interpreting these results.

In order to derive more profound information on the paediatric subset, especially with regards to safety, the MAH has conducted a pooled analysis where a total of 1435 adults and 97 adolescents and children were included in the analysis.

Although the numbers included in the pediatric subset can be deemed to be rather low, the proposal for section 4.8 generally improves the safety for the use of the vaccination by including some new AE for pediatric patients in section 4.8 and providing more accurate frequencies in some AE taking the results for the pediatric subset more into account.

Myalgia was the most frequently reported solicited systemic reaction for all pediatric subjects (14.6%) and in subjects 12 to 17 years of age (27.6%), but the percentages were lower than observed in adults (47.1%) in the pooled analysis. Headache was the most frequently reported solicited systemic reaction in subjects 2 to 11 years of age (11.9%). The most frequently reported adverse reactions in children and adolescents (from 2 to17 years of age) were injection site reactions: pain (52.6%), swelling/oedema/ induration (16.5%) and erythema (14.4%).

In the updated CCDS, the frequency categories of injection site pain, injection site erythema and swelling/induration/edema are listed as “very common” in the pediatric population. The frequency category of fever is listed “common” in the pediatric population.

- **Recommendation**

A type II-variation is requested from the MAH within 2 months after the finalization of the PAR to adopt section 4.8 of the SmPC and section 4 of the PIL in accordance to the agreed wording.

The following **SmPC changes** are proposed in section 4.8:

a. Summary of the safety profile

During clinical development, more than 15,000 people received Typhim Vi (first or second injection).

The most common adverse reaction, in all age groups, was injection site pain. In adults from 18 years of age, myalgia and fatigue were the most frequently reported systemic reactions. In children and adolescents (from 2 to 17 years of age), myalgia and headache were the most frequently reported systemic reactions.

Most adverse reactions appeared with 3 days after vaccination. Most reactions resolved spontaneously within 1 to 3 days after onset.

b. Tabulated list of adverse reactions

The adverse reactions come from clinical studies (pooled analysis) and worldwide post-marketing experience. The pooled analysis has been performed on 6 recent studies sharing the same safety standard integrating data from 1532 subjects (97 children and adolescents from 2 to17 years of age and 1435 adults).

In each System Organ Class, the adverse reactions are ranked under headings of frequency, the most common reactions coming first, using the following convention:

Very common (≥1/10)
Common (≥1/100 to <1/10)

Uncommon (≥1/1000 to <1/100)
Rare (≥1/10 000 to <1/1000)
Very rare (<1/10 000) including isolated cases
Not known (cannot be estimated from the available data).

Adults
(…)

Paediatric population

The table below summarizes the frequencies of the adverse reactions that were recorded after any dose of TYPHIM Vi in children and adolescents (from 2 to17 years of age).

Subjects experiencing at least one: Adverse Reactions	**Children and Adolescents** 2-17 years
	Frequency
Immune system disorders	
Anaphylactic, anaphylactoid reactions, including shock	Not known*
Serum sickness disease	Not known*
Nervous system disorders	
Vasovagal syncope in response to injection	Not known*
Headache	Very common
Respiratory, thoracic and mediastinal disorders	
Asthma	Not known*
Gastrointestinal disorders	
Nausea	Not known*
Vomiting	Not known*
Diarrhoea	Not known*
Abdominal pain	Not known*
Skin and subcutaneous tissue disorders	
Allergic type reactions such as pruritus, rash, urticaria	Not known*
Musculoskeletal and connective tissue disorders	
Arthralgia	Not known*
Myalgia	Very common
General disorders and administration site condition	
Injection site pain	Very common
Injection site erythema	Very common
Injection site swelling/oedema/ induration	Very common
Malaise	Common
Fever	Common
Fatigue/asthenia	Common

* reported during postmarketing surveillance

The most frequently reported adverse reactions in children and adolescents (from 2 to17 years of age) were injection site reactions: pain (52.6%), swelling/oedema/ induration (16.5%) and erythema (14.4%). The most frequently reported systemic reactions were myalgia (14.6%) and headache (13.5%).

The following **PIL changes** are proposed in section 4:

Like all medicines, this vaccine can cause side effects, although not everybody gets them.

Serious allergic reactions:

Anaphylactic, anaphylactoid reactions, including shock which can include one or several of the following symptoms:

- o urticaria, skin rash,
- o swelling of face and/or neck,
- o breathing difficulties, bluish discoloration of the tongue or lips,
- o low blood pressure, rapid heart rate and weak pulse, skin coldness, dizziness and potentially fainting.

When these signs or symptoms appear, it is usually very soon after the injection, while the person affected is still at the clinic or at the doctor's surgery. If one of these symptoms occurs after you have left the place where the injection was administered, you must consult a doctor IMMEDIATELY.

Other side effects reported in adults

(….)

Other side effects reported in children and adolescents (from 2 to 17 years of age):

Very common: may affect more than 1 in 10 people

• Injection site pain, injection site redness (erythema), injection site swelling/oedema, injection site hardening (induration),
• Headache,
• Muscle paint (myalgia),

Common: may affect up to 1 in 10 people

• Generally feeling unwell (malaise),
• Fatigue, unusual weakness (asthenia),
• Fever.

Most side effects reported in adult and children/adolescents appeared within 3 days after vaccination. Most reactions resolved spontaneously within 1 to 3 days after onset.

Not known: frequency cannot be estimated from the available data in adult and children/adolescents

• Serum sickness disease: joint pain, skin rash, enlarged lymph nodes and generally feeling unwell.
When these symptoms appear, it is generally 2-4 weeks after vaccination,
• Fainting in response to injection (vasovagal syncope),
• Cough, wheezing, respiratory discomfort (asthma),
• Nausea, vomiting, diarrhoea, stomach pain (abdominal pain),
• Rash, sometimes swollen and itchy (pruritus, skin rash, urticaria),
• Joint pain (arthralgia).