26 March 2015
EMA/250256/2015
Committee for Medicinal Products for Human Use (CHMP)

Optaflu

(Hemagglutinin Antigen and Neuraminidase Antigen of A/Brisbane/10/2010 (H1N1), A/Texas/50/2012 (H3N2), and B/Massachusetts/2/2012, produced in cell culture)

Procedure no.: EMEA/H/C/000758/P053

Marketing authorisation holder (MAH): Novartis Vaccines and Diagnostics GmbH.

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment report as adopted by the CHMP with all commercially confidential information deleted

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1. Introduction

On 31 December 2014, the MAH submitted a completed paediatric study for Optaflu, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. It concerns the CSR for study V58P15.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that *V58P15 - A Phase III, Observer-Blind, Randomized Multicenter Study to Evaluate the Safety of Trivalent Subunit Influenza Vaccines, Produced Either in Mammalian Cell Culture (TIVc) or in Embryonated Eggs (TIV), in Children and Adolescents 3 to < 18 Years of Age at Risk for Influenza-Related Complications* is part of a clinical development program. It should be noted that the Optaflu PIP (EMEA 000124-PIP01-07-M02) is currently on hold (please refer to http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/10/WC500151670.pdf.

2.2. Information on the pharmaceutical formulation used in the study

Not applicable.

2.3. Clinical aspects

2.3.1. Introduction

Annual influenza epidemics are associated with substantial morbidity and mortality, especially in elderly and in those with underlying diseases. Although in healthy adults clinical influenza infections generally have an uncomplicated course, it may have a substantial economic impact, e.g. due to days lost from work. Vaccination to prevent influenza is particularly important for people who are at high risk for serious complications from influenza.

The main objective of influenza vaccination in elderly is reducing the number of deaths caused by influenza infections. In younger populations, influenza associated morbidity is more important than mortality risk, especially in those at good health. Trivalent influenza vaccines contain an A/H3N2, an A/H1N1 and a B strain component. The selection of the A and B influenza virus strains for the vaccines is based on the annual WHO and Committee for Human Medicinal Products (CHMP) strain recommendations. These viruses are the predominant strains most appropriate to the epidemiological situation in each hemisphere.

Since their development, inactivated influenza vaccines have been produced in the allantoic cavity of embryonated hen eggs. However, the efficiency of the method is low, requiring one or more eggs for each dose of the vaccine produced. The use of mammalian cell lines eliminates the reliance on the supply of embryonated eggs and generates more flexibility, adequate availability of substrate for virus growth and the possibility of higher virus yields. In addition, the cell culture-derived vaccines do not require extensive advance planning and can, in principle, be vital in responding to the threat of an emerging pandemic.

The MAH has developed a cell-derived, trivalent, surface antigen, inactivated influenza vaccine (Optaflu, referred to as TIVc throughout this document) produced in the mammalian cell line Madin Darby Canine Kidney (MDCK). Optaflu is currently registered in the European Union (EU) for prophylaxis of influenza for adults, especially in those who run an increased risk of associated complications and should be used in accordance to official guidance.

The present study is part of the approved EU Paediatric Investigation Plan (PIP) for Optaflu (EMEA-000124-PIP01-07-M02; currently on hold upon request of the MAH, until testing in the pediatric

population can be conducted with the MAH's Quadrivalent cell culture influenza vaccine that is under development).

2.3.2. Clinical study

Study V58P15: *A Phase III, Observer-Blind, Randomized Multicenter Study to Evaluate the Safety of Trivalent Subunit Influenza Vaccines, Produced Either in Mammalian Cell Culture (TIVc) or in Embryonated Eggs (TIV), in Children and Adolescents 3 to < 18 Years of Age at Risk for Influenza-Related Complications.*

Conducted in 16 centers in 2 countries: 12 sites in Spain and 4 sites in Italy.

Study period: 25 October 2013 till 31 July 2014.

Description

Methods

Objective(s)

To evaluate the safety and tolerability of 1 or 2 intramuscular doses (administered 4 weeks apart) of, either the cell culture-derived influenza vaccine (TIVc) or the egg-derived influenza vaccine (TIV) in children and adolescents 3 to <18 years of age, at risk for influenza-related complications.

Study design

This phase 3, randomized, observer blind, multicenter study was performed over a period of approximately 6 to 7 months. Approximately 504 children and adolescents (3 to < 18 years of age) at risk for influenza related complications were planned to be enrolled in the study.

MDCK TIVc (Lot number 035011C) contained the purified viral envelope glycoproteins, hemagglutinin (HA) and neuraminidase (NA), derived from 3 strains (including approximately 15 µg of HA for each strain [A/Brisbane/10/2010 (H1N1) virus antigen, A/Texas/50/2012 (H3N2) virus antigen, and B/Massachusetts/2/2012 virus antigen]) as recommended by the WHO for the 2013-2014 influenza season in the Northern Hemisphere.
Conventional TIV (Lot number IA122002) contained the purified viral envelope glycoproteins, HA and NA, derived from 3 strains (including approximately 15 µg of HA for each strain [A/California/07/2009 NYMC X-181 (H1N1) virus antigen, A/Texas/50/2012 NYMC X-223 (H3N2) virus antigen, and B/Massachusetts/2/2012 wt virus antigen]) as recommended by the WHO for the 2013-2014 influenza season in the Northern Hemisphere.

Study population & Sample size

Study population:
Individuals were males and females 3 to < 18 years of age at the time of enrollment who were at high risk for influenza-related complications. Children were identified as being at risk for influenza-related complications based on confirmed documented medical history of diseases such as endocrine disorders, chronic cardiovascular diseases, chronic pulmonary diseases, chronic renal or hepatic diseases, neurological and neurodevelopmental conditions, blood disorders, metabolic disorders, weak immune system, children who received long term aspirin therapy or obesity.

Sample size:
Approximately 504 subjects were to be randomized to receive 1 or 2 doses of TIVc or TIV according to age and seasonal influenza vaccination status. Assuming that about 10% of the subjects were to be nonevaluable (due to loss of follow-up or protocol deviations, etc.), 450 subjects (300 receiving TIVc and 150 receiving TIV) were to be evaluable for safety. For a sample size of 300 subjects exposed to the TIVc, the probability of observing at least 1 AE will be 95% when the rate of the event is 0.010 (1 in 100), while among the 450 subjects exposed to any of the 2 study vaccines, it will be 99%.

The sample size of this study is also based on the PIP commitment (in accordance with the EMEA/CHMP/VWP/263499/2006 guideline), to establish a total safety database of 300 at risk for influenza related complications subjects, 6 months to < 18 years of age, that received the TIVc. This study with subjects 3 to < 18 years of age was meant to contribute at least 150 and 75 subjects exposed to TIVc and TIV respectively.

Treatments

Eligible subjects were enrolled and randomized in a 2:1 ratio to receive either TIVc or TIV, stratified by age (3 to < 9 years of age and 9 to < 18 years of age) and by previous influenza vaccination status ("previously vaccinated" was defined as any child under 9 years of age who had since 2010 received ≥ 2 doses of seasonal influenza vaccine (group 2); children and adolescents 9 to <18 years of age were considered "previously vaccinated" by default (group 1); "previously not vaccinated" was defined as any child under 9 years of age who does not meet the conditions for "previously vaccinated" (group 3)).

The full vaccination course consisted of either one 0.5 mL dose (groups 1 and 2) of TIVc or TIV on day 1, or two 0.5 mL doses (group 3) of TIVc or TIV administered 4 weeks apart on days 1 and 29.

For each subject in groups 1 and 2, study participation comprised a total of 3 clinic visits, 2 reminder calls, and 4 safety calls through a treatment period and a follow-up period (subject's total participation time was approximately 6 months).

- Treatment period (day 1 through day 29): two clinic visits and 2 reminder calls.
- Follow-up period (day 30 through day 181): one clinic visit and 4 safety calls.

For each subject in group 3, study participation comprised a total of 4 clinic visits, 4 reminder calls, and 4 safety calls through a treatment period and a follow-up period (subject's total participation time was approximately 7 months).

- Treatment period (day 1 through day 57): three clinic visits and four reminder calls.
- Follow-up period (day 58 through day 209): one clinic visit and four safety calls.

All unsolicited AEs were summarized according to medical dictionary for regulatory activities (MedDRA, Version 17.0) system organ class (SOC) and preferred term (PT) within SOC.

Outcomes/endpoints

The primary endpoint for this study is safety. There are no secondary or other endpoints.
The measures for assessing safety and tolerability are as follows:

- Proportion of subjects reporting solicited AEs, including local and systemic and other solicited AEs
- Proportion of subjects reporting unsolicited AEs
- Proportion of subjects reporting SAEs, NOCDs, medically attended AEs, and AEs leading to vaccine/study withdrawal, collected for the whole study

Statistical Methods

Evaluation of the safety endpoints was of descriptive nature without prespecified criteria.

Results

Recruitment/ Number analysed

Out of 504 planned, a total of 430 subjects were enrolled (282 subjects in the TIVc and 148 subjects in the TIV group) in this study. Table 9.1-1 provides the planned and actual number of subjects enrolled in the study per age category per seasonal influenza vaccination status.

Four subjects were enrolled in the study but did not receive study vaccination, they were excluded from the safety sets.

415 subjects completed the study (272 from the TIVc group and 143 from the TIV group. Ten subjects from the TIVc and 5 subjects from the TIV group were prematurely withdrawn from the study. The common reasons for premature withdrawals were withdrawal of consent and subjects being lost to follow up. No safety related reason was reported.

Table 9.1-1 Number of Subjects Planned and Enrolled as per Vaccine Treatment Group According to Age and Seasonal Influenza Vaccination Status

Subject Group	Number of Doses of TIVc or TIV (0.5 mL with 15 µg HA of each strain)	Age Group and Vaccination Status	Influenza Vaccine			
			TIVc		TIV	
			Planned	Enrolled	Planned	Enrolled
Group 1	1 dose	9 to < 18 years, previously vaccinated	168	143	84	74
Group 2	1 dose	3 to < 9 years, previously vaccinated	~60* to 108	54	~30* to 54	35
Group 3	2 doses	3 to < 9 years, not previously vaccinated	~60* to 108	86	~30* to 54	39
		Total	336	283	168	148

CHMP's comment:

The number of subjects enrolled in the present study was lower than planned (430 enrolled vs 504 planned), due to late availability of vaccine and unforeseen reluctance of subjects to participate in the trial. It was however enough to reach the MAH's goal to contribute at least 150 and 75 subjects exposed to TIVc and TIV respectively, in order to establish a total safety database of 300 at risk for influenza related complications subjects, 6 months to < 18 years of age, that received TIVc. Differences in events that occur in 4% or more of the population can be detected with the enrolled sample size.

Baseline data

Demographic and baseline characteristics were comparable in both vaccine groups (TIVc and TIV). The average age of the subjects at study entry in TIVc group was 8.7 ± 4.0 years and 9.0 ± 3.9 years in TIV group. Most of the enrolled subjects were from Spain and were of White origin in both vaccine groups. All subjects enrolled met the entry criteria (Table 11.2-1).

Table 11.2-1 Demographic and Other Baseline Characteristics in Subjects 3 to < 18 Years of Age – Enrolled Set

	TIVc N= 282	TIV N= 148
Age (Years, Mean ± SD)	8.7 ± 4.0	9.0 ± 3.9
3 to < 9 years, Not previously vaccinated	86 (30%)	39 (26%)
3 to < 9 years, previously vaccinated	54 (19%)	35 (24%)
9 to < 18 years, previously vaccinated	142 (50%)	74 (50%)
Gender:		
Female	121 (43%)	63 (43%)
Male	161 (57%)	85 (57%)
Race		
Asian	2 (<1%)	2 (1%)
Black or African American	3 (1%)	4 (3%)
White	250 (89%)	131 (89%)
Other	27 (10%)	11 (7%)
Ethnic origin:		
Hispanic or Latino	35 (12%)	23 (16%)
Not Hispanic or Latino	247 (88%)	125 (84%)
Weight (kg):	35.64 ± 18.47	35.85 ± 16.43
Height (cm):	133.2 ± 23.5	133.8 ± 22.9
Country		
Italy	66 (23%)	37 (25%)
Spain	216 (77%)	111 (75%)
Met entry criteria:		
Yes	282 (100%)	148 (100%)

CHMP's comment:

Overall the baseline characteristics of the two vaccine groups were similar. Except for the 3 to < 9 years age group in the TIVc group, where more children were not previously vaccinated (30% vs 19% previously vaccinated). In the TIV group this was more balanced (26% vs 24%). As the number of subjects in the 3 to < 9 years, previously vaccinated group (n=54) is still sufficient, this most likely will not impact the results of the study. Moreover, all safety data is presented per age and vaccination status subgroup so there is no bias in results due to this difference in vaccination status between the two vaccine groups.

Efficacy results

Not applicable.

Safety results

Of the total 430 subjects enrolled in this study, 426 subjects (278 subjects received TIVc and 148 subjects received TIV) were exposed to at least 1 study vaccination and were considered for safety analysis.

All exposed subjects (N= 426) provided safety data at least for 1 time point and were included in the overall safety set. One subject from the TIVc treatment group and 2 subjects from the TIV treatment

group did not provide any postvaccination solicited safety data collected between day 1 though day 7; these subjects were not included in the solicited AE safety dataset. All 3 subjects belonged to 9 to < 18 years age sub group. All exposed subjects (N= 426) provided postvaccination unsolicited data and were included in the unsolicited safety data set.

- **Proportion of subjects reporting solicited AEs, including local and systemic and other solicited AEs**

The percentage of subjects who reported any solicited AE in both the TIVc and TIV group was 73%. Percentages were higher after the first (TIVc: 70% [N = 277], TIV: 72% [N = 146]) than after the second vaccination (TIVc: 59% [N = 83], TIV: 53% [N = 40]) in both vaccine groups (Table 2.5.5-2).

Solicited local AEs were reported by 59% of subjects in the TIVc and 62% of subjects in the TIV groups. Percentages of subjects who reported solicited systemic AEs were 46% in the TIVc and 40% in the TIV groups (Table 2.5.5-2).

After the first vaccination, the percentages of subjects who reported solicited local AEs were 54% in the TIVc and 61% in the TIV groups and systemic AEs were reported for 42% of subjects in the TIVc and 38% of subjects in the TIV groups. After the second vaccination, the percentage of subjects who reported solicited local AEs were 49% and 45% in the TIVc and TIV groups, respectively. The percentage of subjects who reported solicited systemic AEs after second vaccination was higher in the TIVc group (35%) than in the TIV group (20%) (Table 2.5.5-2).

Table 2.5.5-2 **Overview of Solicited AEs After Each/Any Vaccination (Day 1 [6 h] Through Day 7 [Dose 1] and Day 29 Through Day 35 [Dose 2]) in Subjects 3 to < 18 Years of Age - Safety Set Solicited AEs**

	Number (%) of Subjects					
	TIVc			TIV		
	Dose 1 N= 277	Dose 2 N=83	Any Dose N=277	Dose 1 N=145	Dose 2 N=40	Any Dose N=146
Any Solicited AE	193 (70)	49 (59)	202 (73)	105 (72)	21 (53)	107 (73)
Local	149 (54)	41 (49)	163 (59)	89 (61)	18 (45)	91 (62)
Systemic*	117 (42)	29 (35)	128 (46)	55 (38)	8 (20)	58 (40)

Analysis of solicited AEs by age group

Subjects 3 to < 6 years of age
The most commonly reported solicited local AE in both previously vaccinated and previously not vaccinated subjects 3 to < 6 years of age in both vaccine groups was injection site tenderness. Two subjects, both previously vaccinated and in the TIV group, reported a severe solicited local AE; one subjects reported severe injection site erythema, one subject reported severe injection site induration (Table 12.2.3-1).

The most commonly reported solicited systemic AE in both previously vaccinated and previously not vaccinated subjects 3 to < 6 years of age in both vaccine groups after the first vaccination was irritability, change in eating habits and fever. After the second vaccination subjects in the TIVc and TIV groups reported most commonly change in eating habits, sleepiness and irritability. Two previously vaccinated subjects, both in the TIV group, and one previously not vaccinated subject, in the TIVc group, reported a severe solicited systemic AE; two subjects reported severe chills, one subject reported severe irritability (Table 12.2.3-4).

Table 12.2.3-1 Numbers (%) of Subjects with Any (And Severe / > 50 mm) Local AEs from Day 1 (6 Hours) Through Day 7 (Post Injection 1) and Day 29 Through Day 35 (Post Injection 2) Reported in Children 3 to <6 Years of Age – Safety Set Solicited AEs

Vaccine Groups		TIVc			TIV		
Vaccination Status		Previously Vaccinated	Previously Not Vaccinated		Previously Vaccinated	Previously Not Vaccinated	
No. of Doses		Injection 1	Injection 1	Injection 2	Injection 1	Injection 1	Injection 2
		N = 28	N = 50	N = 50	N = 19	N = 15	N = 15
Any solicited local AE		14 (50%)	19 (38%)	22 (44%)	12 (63%)	7 (47%)	7 (47%)
Injection site tenderness	Any	10 (36%)	15 (31%) N = 49	20 (41%) N = 49	11 (58%)	6 (40%)	6 (40%)
	Severe[a]	0	0	0	0	0	0
Injection site erythema (mm)	Any	7 (26%) N = 27	1 (2%)	3 (6%)	4 (22%) N = 18	0	4 (27%)
	>50 mm	0	0	0	1 (6%)	0	0
Injection site induration (mm)	Any	2 (7%)	5 (10%)	5 (10%)	2 (11%)	2 (13%)	3 (20%)
	>50mm	0	0	0	1 (5%)	0	0
Injection site ecchymosis (mm)	Any	2 (7%) N = 27	4 (8%)	1 (2%)	2 (11%)	1 (7%)	3 (20%)
	>50mm	0	0	0	0	0	0

Table 12.2.3-4 Number (%) of Subjects with Any Solicited Systemic AEs and Other AEs from Day 1 (6 Hours) Through Day 7 (Post Injection 1) and Day 29 Through Day 35 (Post Injection 2) Reported in Children 3 to < 6 Years of Age –Safety Set Solicited AEs

Vaccine Group		TIVc			TIV		
Vaccination Status		Previously Vaccinated	Previously Not Vaccinated		Previously Vaccinated	Previously Not Vaccinated	
No. of Doses		Injection 1	Injection 1	Injection 2	Injection 1	Injection 1	Injection 2
		N = 28	N = 50	N = 50	N = 19	N = 15	N = 15
Systemic							
Any solicited systemic AE		10 (36%)	22 (44%)	14 (28%)	9 (47%)	5 (33%)	5 (33%)
shivering/chills	Present	2 (7%)	5 (10%)	3 (6%) N = 48	2 (11%)	0	0 N= 14
Change in eating habits	Present	5 (18%)	7 (14%)	6 (12%)	3 (16%)	4 (27%)	2 (13%)
Sleepiness	Present	4 (14%)	6 (12%) N = 49	5 (10%) N = 48	3 (16%)	0	2 (13%)
Irritability	Present	6 (21%)	8 (16%) N = 49	5 (10%) N = 48	5 (26%)	2 (13%)	2 (13%)
Vomiting	Present	3 (11%)	4 (8%)	2 (4%)	1 (5%)	0	1 (7%)
Diarrhea	Present	3 (11%)	1 (2%)	1 (2%)	1 (5%)	0 N= 14	2 (13%)
Fever (body temperature ≥ 38 °C)	Yes	4 (15%) N = 27	8 (16%) N = 49	2 (4%)	3 (16%)	0	0

CHMP's comment:

In the previously not vaccinated 3 to < 6 years age subgroup fever rates were 16% in the TIVc group compared to 0% in the TIV group after first vaccination. With second vaccination, the fever rates were 4% and 0% in these vaccine groups. Fever rates were similar between previously vaccinated vaccine groups (15% and 16% in the TIVc and TIV groups respectively). These differences are most likely due to the relatively small sample size.

Subjects 6 to < 9 years of age

The most commonly reported solicited local AE in both previously vaccinated and previously not vaccinated subjects in both vaccine groups was injection site pain. One previously not vaccinated subject, in the TIVc group, reported a severe solicited local AE; injection site pain after the second vaccination (Table 12.2.3-2).

The most commonly reported solicited systemic AEs were myalgia, headache, chills, arthralgia, nausea, loss of appetite and fatigue. One subject, previously not vaccinated and in the TIVc group, reported a severe local systemic AE; severe myalgia after the second vaccination (Table 12.2.3-3).

Table 12.2.3-2 Numbers (%) of Subjects with Any (And Severe > 100 mm) Local AEs from Day 1 (6 Hours) Through Day 7 (Post Injection 1) and Day 29 Through Day 35 (Post Injection 2) Reported in Children ≥ 6 to < 9 Years of Age – Safety Set Solicited AEs

Vaccine Group		TIVc			TIV		
Vaccination Status		Previously Vaccinated	Previously Not Vaccinated		Previously Vaccinated	Previously Not Vaccinated	
No. of Doses		Injection 1	Injection 1	Injection 2	Injection 1	Injection 1	Injection 2
		N = 26	N = 35	N = 33	N = 16	N = 23	N = 24
Any solicited local AE		16 (62%)	19 (54%)	19 (58%)	8 (50%)	13 (57%)	11 (46%)
Injection site pain	Any	15 (58%)	18 (56%) N = 32	19 (61%) N = 31	8 (50%)	10 (45%) N = 22	8 (36%) N = 22
	Severe	0	0	1 (3%)	0	0	0
Injection site erythema (mm)	Any	1 (4%)	3 (9%) N = 34	5 (16%) N = 32	4 (25%)	5 (22%)	3 (13%) N = 23
	>100 mm	0	0	0	1 (6%)	0	0
Injection site induration (mm)	Any	1 (4%)	4 (12%) N = 34	3 (9%) N = 32	3 (19%)	2 (9%)	3 (13%) N = 23
	>100 mm	0	0	0	1 (6%)	0	0
Injection site ecchymosis (mm)	Any	2 (8%)	3 (9%) N = 34	2 (6%) N = 32	0	3 (14%) N = 22	5 (22%) N = 23
	>100 mm	0	0	0	0	0	0

Table 12.2.3-5 **Number (%) of Subjects with Any and, Where Relevant, Severe Solicited Systemic AEs and Other AEs from Day 1 (6 Hours) Through Day 7 (Post Injection 1) and Day 29 Through Day 35 (Post Injection 2) Reported in Children ≥ 6 to < 9 Years of Age – Safety Set Solicited AEs**

Vaccine Group		TIVc			TIV		
Vaccination Status		Previously Vaccinated	Previously Not Vaccinated		Previously Vaccinated	Previously Not Vaccinated	
No. of Doses		Injection 1	Injection 1	Injection 2	Injection 1	Injection 1	Injection 2
		N = 26	N = 35	N = 33	N = 16	N = 23	N = 24
Systemic AEs*		9 (35%)	18 (51%)	15 (45%)	5 (31%)	5 (22%)	3(13%)
Chills	Any	3 (12%) N = 25	3 (9%) N = 33	3 (10%) N = 31	1 (6%)	0 N = 22	0 N= 23
	Severe	0	0	0	0	0 N = 22	0 N= 23
Nausea	Any	1 (4%)	3 (9%) N = 32	0 N = 30	2 (13%)	0 N= 20	0 N= 21
	Severe	0	0	0 N= 30	0	0 N= 20	0 N= 21
Myalgia	Any	4 (15%)	2 (6%) N = 32	5 (17%) N = 30	2 (13%)	1 (5%) N = 20	0 N= 21
	Severe	0	0	1 (3%%) N= 30	0	0	0 N= 21
Arthralgia	Any	2 (8%)	4 (13%) N = 32	0 N= 30	1 (6%)	1 (5%) N = 20	0 N= 21
	Severe	0	0	0 N= 30	0	0	0 N= 21
Headache	Any	1 (4%)	5 (16%) N = 32	8 (27%) N = 30	3 (19%)	2 (10%) N = 20	1 (5%) N = 21
	Severe	0 (%)	0	0	0	0	0
Fatigue	Any	2 (8%)	3 (9%) N = 32	4 (13%) N = 30	2 (13%)	0 N= 20	0 N= 21
	Severe	0	0	0	0	0 N= 20	0 N= 21
Loss of Appetite	Any	2 (8%)	8 (25%) N = 32	5 (16%) N = 31	2 (13%)	2 (9%) N = 22	2 (9%) N = 23
	Severe	0	0	0	0	0	0
Diarrhea	Any	1 (4%)	3 (9%) N = 33	1 (3%) N = 31	0	0 N= 22	1 (4%) N = 23
	Severe	0	0	0	0	0 N= 22	0
Vomiting	Any	0	3 (9%) N = 33	1 (3%) N = 31	1 (6%)	0 N= 22	0 N= 23
	Severe	0	0	0	0	0 N= 22	0 N= 23
Fever (body temperature ≥ 38°C)	Yes	1 (4%)	1 (3%) N = 34	0	0	0	0

CHMP's comment:

Injection site erythema and ecchymosis were more common in TIV vaccinated compared to TIVc vaccinated subjects. The latter group reported more frequently injection site pain. More solicited systemic AEs were reported in the TIVc compared with the TIV previously not vaccinated group (51% and 45% after injection 1 and 2 for TIVc vs 22% and 13% for TIV). Differences were most notably in chills, headache and fatigue, but interpretation of these results should be done with caution due to the small sample size.

Subjects 9 to < 18 years of age

The most commonly reported solicited local AE in both the TIVc and TIV group was injection site pain (53% and 65% of subjects, respectively). Nine subjects (4 subjects in TIVc group and 5 subjects in TIV group) reported severe solicited local AEs (Table 12.2.3-3).

The most commonly reported solicited systemic AE was headache, followed by myalgia and fatigue. Overall, 15 subjects (11 subjects in TIVc group and 4 subjects in TIV group) reported severe solicited systemic AEs (Table 12.2.3-6).

Table 12.2.3-3 Numbers (%) of Subjects with Any (And Severe / > 100 mm) Local AEs from Day 1 (6 Hours) Through Day 7, Reported in Previously Vaccinated Children 9 to < 18 Years of Age – Safety Set Solicited AEs

Vaccine group		TIVc N = 138	TIV N = 72
Any solicited local AE			
Injection site pain	Any	73 (53%)	47 (65%)
	Severe	1 (1%)	1 (1%)
Injection site erythema (mm)	Any	5 (4%) N = 131	2 (3%) N = 61
	Severe	2 (2%)	0
Injection site induration (mm)	Any	6 (5%) N = 127	7 (11%) N = 61
	Severe	1 (1%)	4 (7%)
Injection site ecchymosis	Any	0 N = 135	0 N = 69
	Severe	0	0

Table 12.2.3-6 Number (%) of Subjects with Any and, Where Relevant, Severe Solicited Systemic AEs and Other AEs from Day 1 (6 Hours) Through Day 7 Reported in Previously Vaccinated Children 9 to < 18 Years of Age – Safety Set Solicited AEs

Vaccine groups		TIVc	TIV
		N = 138	N = 72
Systemic		58 (42%)	31 (43%)
Chills	Any	19 (14%)	6 (8%)
	Severe	1 (1%)	0
Nausea	Any	17 (12%) N = 137	10 (14%)
	Severe	2 (1%) N= 137	2 (3%)
Myalgia	Any	29 (21%)	11 (15%)
	Severe	1 (1%)	0
Arthralgia	Any	18 (13%) N = 136	7 (10%)
	Severe	1 (1%) N= 136	0
Headache	Any	29 (21%)	19 (26%)
	Severe	1 (1%)	1 (1%)
Fatigue	Any	23 (17%) N = 137	14 (19%)
	Severe	2 (1%) N= 137	1 (1%)
Loss of Appetite	Any	20 (14%)	12 (17%)
	Severe	1 (1%)	0
Diarrhea	Any	11 (8%) N = 137	4 (6%) N = 71
	Severe	0 N= 137	0 N= 71
Vomiting	Any	8 (6%)	3 (4%)
	Severe	2 (1%)	0
Fever (body temperature ≥ 38 °C)	Yes	4 (3%) N = 137	3 (4%)

CHMP's comment:

Severe injection site induration was more frequently reported by TIV vaccinated subjects compared with TIVc vaccinated subjects (7% vs 1%, respectively).

Overall, subgroup analyses by gender (male/female) and by race/ethnicity (white [not Hispanic or Latino]/other) did not show any meaningful differences in percentage of subjects reporting solicited AEs and unsolicited AEs after any vaccination between both vaccine groups.

CHMP's comment:

Overall, the most common solicited local AEs related to discomfort at the vaccination site in all age groups. The majority of the solicited AEs were mild or moderate in severity and they resolved within seven days. None of the subjects reported body temperature of ≥ 40° C in either the TIVc or TIV treatment groups. Within the age and vaccination status subgroups, some differences in solicited local and systemic AEs were observed between the vaccine groups but a consistent pattern was not observed.

- **Proportion of subjects reporting unsolicited AEs**

Overall, 77% of subjects in the TIVc group and 75% of subjects in the TIV group reported any unsolicited AE. Unsolicited AEs that were assessed as possibly or probably related to the study vaccine were reported by 16 subjects (6%) and 12 subjects (8%) in the TIVc and TIV groups, respectively (Table 2.5.5-4).

Table 2.5.5-4 Overview of Unsolicited AEs by Age Group and Previous Vaccination Status - Safety Set Unsolicited AEs

	Number (%) of Subjects							
	TIVc				TIV			
	Not Previously Vaccinated	Previously Vaccinated		All	Not Previously Vaccinated	Previously Vaccinated		All
	3 to < 9 N = 85	3 to < 9 N = 54	9 to < 18 N = 139	3 to < 18 N = 278	3 to < 9 N = 39	3 to < 9 N = 35	9 to < 18 N = 74	3 to < 18 N = 148
Any AE	77 (91)	46 (85)	90 (65)	213 (77)	32(82)	29 (83)	[illegible]	111 (75)
Possibly/Probably Related	7 (8)	3 (6)	7 (5)	17 (6)	5 (13)	3 (9)	[illegible]	12 (8)
SAE	4 (5)	2 (4)	6 (4)	12 (4)	0	2 (6)	[illegible]	4 (3)
Possibly/Probably Related	0	0	0	0	0	0	0	0
NOCD	1 (1)	0	2 (1)	3 (1)	0	1 (3)	0	1 (1)
Medically Attended AEs	71 (84)	38 (70)	78 (56)	187 (67)	28 (72)	24 (69)	42 (57)	94 (64)
AEs Leading to Withdrawal	0	0	0	0	0	0	0	0
Death[a]	0	0	0	0	0	0	0	0

Abbreviations: AE = adverse event. SAE = serious adverse event. NOCD = new onset of chronic disease.
[a] One death was reported, but as this was reported a few days after database lock it is not reflected in the database. This death was assessed by the investigator as not related to the study vaccine (see CSR V58P15, Section 12.3.1.1 for more details).

CHMP's comment:

Although overall the percentage of subjects reporting unsolicited AEs were similar in the TIVc and TIV groups, the percentage of subjects reporting unsolicited AEs was higher in the younger age group (3 to < 9) compared with the older age group (9 to < 18).

In both the TIVc and TIV treatment groups, during 28 day follow-up after each vaccination, the most commonly affected SOC was infections and infestations reported for 9% and 16% of subjects, respectively, followed by respiratory, thoracic and mediastinal disorders, general disorders and nervous system disorders (Table 12.2.3-7).

Table 12.2.3-7 **Number (%) of Subjects with Any Unsolicited Adverse Events During 28 Day Follow-Up After Each Vaccine Dose By System Organ Class, in Subjects 3 to < 18 Years of Age; TIVc and TIV Vaccine Group**

	TIVc				TIV			
	Previously Not Vaccinated	Previously Vaccinated		Total	Previously Not Vaccinated	Previously Vaccinated		Total
SOC Preferred term	3 to < 9 Years N = 85	3 to < 9 Years N = 54	9 to < 18 Years N = 139	3 to < 18 Years N = 278	3 to <9 Years N = 39	3 to <9 Years N = 35	9 to < 18 Years N = 74	3 to < 18 Years N = 148
	Any	Any	Any	Any	Any	Any	Any	Any
Any AE	28 (33%)	18 (33%)	16 (12%)	44 (16%)	14 (36%)	20 (57%)	9 (12%)	35 (24%)
Nervous system disorders	1 (1%)	2 (4%)	NA	3 (1%)	2 (5%)	1 (3%)	NA	4 (3%)
Ear and labyrinth disorders	3 (4%)	0	NA	NA	0	1 (3%)	NA	NA
Psychiatric disorders	NA	1 (2%)	NA	NA	NA	0	NA	NA
Skin and subcutaneous tissue disorders	NA	4 (7%)	NA	NA	NA	1 (3%)	NA	NA
Musculoskeletal disorder	NA	1 (2%)	NA	NA	NA	1 (3%)	NA	NA
Gastrointestinal disorders	0	1 (2%)	3 (2%)	NA	1 (3%)	0	1 (1%)	NA
General disorders and administration site conditions	6 (7%)	3 (6%)	0	9 (3%)	3 (8%)	4 (11%)	2 (3%)	3 (2%)
Infections and infestations	17 (20%)	9 (17%)	5 (4%)	26 (9%)	9 (23%)	2 (5%)	4 (5%)	23 (16%)
Metabolism and nutrition disorders	0	1 (2%)	NA	NA	1 (3%)	NA	NA	NA
Injury, poisoning and procedural complications	NA	0	3 (2%)	NA	NA	1 (3%)	0	NA
Musculoskeletal and connective tissue disorders	NA	1 (2%)	NA	NA	NA	1 (3%)	NA	NA
Respiratory, thoracic and mediastinal disorders	7 (8%)	4 (7%)	6 (4%)	10 (4%)	2 (5%)	3 (9%)	4 (5%)	7 (5%)

CHMP's comment:

Irrespective of the specific vaccine, the percentage of subjects reporting any unsolicited AE was higher in the younger age group (3 to < 9) compared with the older age group (9 to < 18). More subjects in the TIV previously vaccinated 3 to <9 group reported unsolicited AEs compared with the TIVc previously vaccinated 3 to <9 group (57% vs 33%, respectively), mostly due to more reports of infections and infestations (34% vs 17%).

In the gender and race subgroup analysis, no significant differences were observed between TIVc and TIV groups, in percentage of subjects reporting unsolicited AEs after any vaccination.

- **Proportion of subjects reporting SAEs, NOCDs, medically attended AEs, and AEs leading to vaccine/study withdrawal, collected for the whole study**

In total, 16 subjects reported at least one SAE during the study (4% and 3% of subjects in the TIVc and TIV group, respectively). The most frequently reported SAEs were under SOC infection and infestations for both the TIVc and the TIV treatment groups (2% and 1% of subjects, respectively). None of the SAEs were assessed as related to the study vaccine (Table 12.3-1).

Table 12.3-1 Number (%) of Subjects with Any Serious Adverse Event Reported From Day 1 Through Study Termination (Day 181/Day 209) in Subjects 3 to < 18 Years of Age

Vaccine Groups	TIVc				TIV			
Vaccination Status	Previously Not Vaccinated	Previously Vaccinated		Combined	Previously Not Vaccinated	Previously Vaccinated		Combined
	3 to < 9 Years	3 to < 9 Years	9 to < 18 Years	3 to < 18 Years	3 to < 9 Years	3 to < 9 Years	9 to < 18 Years	3 to < 18 Years
	N = 85	N = 54	N = 139	N = 278	N = 39	N = 35	N = 74	N = 148
Any SAE	4 (5%)	2 (4%)	6 (4%)	12 (4%)	0	2 (6%)	2 (3%)	4 (3%)
Blood and lymphatic systemdisorders	NA	NA	1 (1%)	1 (< 1%)	NA	NA	0	0
Congenital, familial and genetic disorders	1 (1%)	NA	NA	1 (< 1%)	0	NA	NA	0
Gastrointestinal disorders	NA	0	1 (1%)	1 (< 1%)	NA	1 (3%)	0	1 (1%)
Infections and infestations	2 (2%)	NA	3 (2%)	5 (2%)	0	NA	1 (1%)	1 (1%)
Respiratory, thoracic and mediastinal disorders	1 (1%)	1 (2%)	1 (1%)	3 (1%)	0	0	1 (1%)	1 (1%)
Injury, poisoning and procedural complications	NA	0	NA	0	NA	1 (3%)	NA	1 (1%)
Metabolism and nutrition disorders	NA	0	1 (1%)	1 (< 1%)0	NA	1 (3%)	0	1 (1%)
Nervous systemdisorders	NA	1 (2%)	1 (1%)	2 (1%)	NA	0	0	0
Psychiatric disorders	NA	NA	1 (1%)	1 (< 1%)	NA	NA	0	0
Vascular disorders	NA	NA	1 (1%)	1 (< 1%)	NA	NA	0	0

SAEs, medically attended AEs, and NOCD, were reported in similar percentages of subjects in both TIVc and TIV groups (Table 2.5.5-4). No subject was withdrawn from the study because of AEs and none of the reported SAEs was considered as possibly related to the study vaccines. No death was reported in any treatment group during the study period. However, one 4-year-old (at enrollment) white male subject (not previously vaccinated TIVc treatment group) died 2 weeks after his last study visit. The death was assessed as not related to the study vaccine.

Overall safety

CHMP's comment:

Within the age and vaccination status subgroups, some differences in AEs were observed between TIVc and TIV. As no consistent pattern could be observed these differences are most likely due to small sample size and may not be clinically relevant.

The safety results are in line with the currently known safety profile of TIVc and no new safety signals were identified. It is agreed that the SAEs were considered not possibly or probably related to the study vaccines.

Note: 39 subjects were vaccinated with a study vaccine which was stored with inadequate temperature recording. For this reason, a robustness analysis was performed, excluding the 39 subjects. The percentage of subjects reporting any solicited and unsolicited AEs in the combined TIVc and TIV treatment groups without the 39 subjects was comparable to the percentage that included the 39 subjects. Therefore, excluding the subjects who received vaccine that had been inappropriately stored had no effect on the overall analysis for the total group.

2.5.3. Discussion on clinical aspects

The study described the safety and tolerability of one or two doses (administered 4 weeks apart) of TIVc and TIV in children and adolescents 3 to < 18 years of age at risk for influenza-related complications. Immunogenicity was not assessed in this study.

Overall the TIVc and TIV vaccines were well-tolerated. Most solicited and unsolicited AEs were mild to moderate in intensity, and transient in nature, most resolved within 7 days after vaccination. None of

the subjects were withdrawn from the study because of AEs and none of the reported SAEs were considered related to the study vaccines.

Discomfort at the vaccination site was the commonest solicited local AE with few being in the severe category. None of the subjects reported body temperature of $\geqslant 40^{\circ}$ C in either the TIVc or TIV treatment groups. Within the age and vaccination status subgroups, some differences in solicited local and systemic AEs were observed between the vaccine groups, but a consistent pattern was not observed. These differences are most likely due to the relatively small sample size of the study and may not be medically significant.

Percentages of subjects reporting any unsolicited AE was higher in the younger age group (3 to < 9) compared with the older age group (9 to < 18). The most commonly affected SOC for unsolicited AEs during the 28 days following each vaccination was infections and infestations. More subjects in the TIV previously vaccinated 3 to <9 group reported unsolicited AEs compared with the TIVc previously vaccinated 3 to <9 group (57% vs 33%, respectively), mostly due to more reports of infections and infestations (34% vs 17%). However, again these differences are most likely due to the relatively small sample size of the study and may not be medically significant.

Of note, the MAH recently also submitted the results of study V58_31, evaluating the safety profile of TIVc (Optaflu) and TIVf (Fluvirin) in healthy children and adolescents ≥4 to ≤17 years of age. Compared to healthy children in study V58_31, the percentage of subjects reporting solicited AEs was slightly higher in the present study (73% compared to approximately 65% in V58_31). However, the percentage of unsolicited adverse events, SAEs and medically attended AEs reported in the present study is approximately twice as high compared to V58_31. This might not be unexpected, as the present study enrolled children who were at high risk for influenza-related complications, including children with chronic diseases, neurological and neurodevelopmental conditions, or weak immune system. In both studies, the most frequently reported unsolicited AEs were under SOC infection and infestations. The underlying medical conditions, as well as the treatment of these conditions, most likely resulted in more adverse events after immunisation, as these children in general have an increased risk of infections. Moreover, there is a bias in race between the two studies, as the majority of subjects in V58_31 were Asians (65%) whereas the majority of subjects in the present study were whites (89%). This might further complicate the comparison of the results of these studies.

Overall, the safety results from study V58P15 in children and adolescents 3 to < 18 years of age at risk for influenza-related complications are in line with the known safety profile of TIVc.

3. CHMP's overall conclusion and recommendation

Overall conclusion

The safety results from study V58P15 in children and adolescents 3 to < 18 years of age at risk for influenza-related complications are in line with the known safety profile of TIVc. As the study did not achieve its enrolment target, only differences in events that occur in 4% or more of the population can be detected. The majority of AEs were mild or moderate in severity and none of the SAEs reported in this study was judged by the investigator as possibly or probably related to the study vaccine. The percentage of unsolicited adverse events, SAEs and medically attended AEs reported in the present study is approximately twice as high as compared to study V58_31 in healthy children. No new safety signals were identified.

The results from study V58P15 do not impact the positive benefit-risk profile of TIVc.

As also mentioned in the previous Article 46 submission for Optaflu (EMEA/H/C/000758), it is noted that the current SmPC states that no data in the paediatric population is available. The MAH is requested to provide a proposal for a sentence under the relevant section in 5.1, stating the availability and relevance of the limited data obtained in the paediatric population so far, including both the results from study V58_31 in healthy children and the results from the present study in children at risk for influenza-related complications.

Recommendation

☐ **Fulfilled:**

☒ **Not fulfilled:**

The MAH is requested to provide a proposal for a sentence under the relevant section in 5.1 of the SmPC, stating the availability and relevance of the limited data obtained in the paediatric population so far.

Additional clarifications requested

1. With regard to the current SmPC, it is noted that the SmPC now states that no data in the paediatric population is available. The MAH is requested to provide a proposal for a sentence under the relevant section in 5.1, stating the availability and relevance of the limited data obtained in the paediatric population so far, including both the results from study V58_31 in healthy children and the results from the present study in children at risk for influenza-related complications.