

**Pharmacovigilance Review Memorandum**  
**Office of Biostatistics and Epidemiology/Division of Epidemiology (OBE/DE)**

BLA/Supplement Number:	125408
Subject:	Pharmacovigilance Plan Review
Product Name:	Influenza vaccine (cell-culture derived trivalent influenza vaccine, cTIV), formerly Optaflu
Sponsor:	Novartis Vaccines and Diagnostics, Inc.
Proposed Indication(s):	For active immunization of persons 18 years and older against influenza disease caused by influenza virus subtypes A (both H3N2 and H1N1) and B contained in the vaccine.
Date(s):	CBER receipt date: 22Nov2011; ADD 21Sep2012; PVP dated: May 2011
Submission type:	New BLA
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## 1. Introduction

### a. Product description

Novartis cell-derived influenza vaccine, referred to in this memo as either Optaflu or cTIV, is a trivalent influenza vaccine containing 15 micrograms of hemagglutinin for each of 3 influenza strains: H1N1, H3N2, and influenza B. The vaccine is made using Madin Darby Canine Kidney Cells (MDCK). Unlike all currently approved influenza vaccines, Optaflu does not utilize eggs in the vaccine production process. The vaccine is presented in 0.5cc pre-filled syringes and the sponsor is seeking an indication for the active immunization of persons 18 years of age and older against influenza disease caused by the strains contained in the vaccine. (BLA 1.2 Cover letter, 31Oct2011)

### b. Pertinent regulatory history

#### i. Prior licensure in the US or other nations

##### 1. Summary of indications and usage

Optaflu was authorized in the EU on 1Jun2007 and was first launched in Germany in 2008. (BLA 1.16 EU Risk Management Plan, version 2.0, p1-3) The BLA for Optaflu was filed for review by CBER on 22Nov2011. One of the issues in the development process was the possible safety issues related to the use of MDCK cells. This was addressed at a Vaccine and Related Biological Products Advisory Committee (VRBPAC) meeting in November 2005. Based on this meeting, CBER concluded that the safety of this cell line was sufficiently established that studies could proceed to phase 3. These studies have now been completed and the sponsor is seeking approval.

##### 2. Major postmarketing safety findings

According to the Risk Management Plan, “no confirmed spontaneous cases had been received by Pharmacovigilance Novartis Vaccines & Diagnostics.” Post-marketing experience with Novartis cTIV is limited, consisting of ----(b)(4)----- sold in Germany in 2008. (BLA 1.16 Risk Management Plan, p9)

#### ii. CBER Complete Response letters

None.

#### iii. Relevant prior Advisory Committee meetings

As noted above, the VRBPAC met in November 2005 to assess the safety of using MDCK cells in the production of Novartis cTIV.<sup>1</sup>

### c. Objectives/scope of this review

The purpose of this review is to identify potential safety issues that may need to be addressed through post-marketing safety surveillance or studies should the product be licensed and to assess the adequacy of the submitted pharmacovigilance plan. Note that although final study reports were submitted for three age groups: (a) adults aged 18 – 64 years, (b) older adults aged >64 years, and (c) pediatric patients aged 3 – 17 years, the sponsor is only seeking an

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<sup>1</sup> Background information provided to the VRBPAC on MDCK cells and their use in vaccines can be found at: [http://www.fda.gov/ohrms/dockets/ac/05/briefing/5-4188B1\\_3.htm](http://www.fda.gov/ohrms/dockets/ac/05/briefing/5-4188B1_3.htm)

indication for the ages 18 years and older. Accordingly, the safety and PVP assessments will focus primarily on this indication.

## **2. Materials reviewed**

### **a. Routine items**

#### **i. Pharmacovigilance Plan**

EU Risk Management Plan, version 2.0, May 2011.

#### **ii. Pertinent sections of the BLA selected by the reviewer**

BLA section 1.2 Cover letter, 31Oct2011

BLA section 1.11.2 Safety Information Amendment

BLA section 2.5 Clinical Overview

BLA section 2.7.4 Summary of Clinical Safety

BLA 5.3.5.1 V58P9 Final Clinical Study Report

BLA 5.3.5.1 V58P13 Final Clinical Study Report

#### **iii. Input from CBER Clinical and statistical reviewers**

1. Email communication with clinical reviewer, Melisse Baylor.

2. Review of her slide presentation, "Optaflu: Mid-cycle Meeting Clinical Review," April 11, 2012

### **b. Other items**

#### **i. Advisory committee reviews**

VBRPAC meeting, Summary Minutes of Meeting #104, Nov16-17, 2005<sup>2</sup>  
Background Summary for the Nov 16, 2005 VRBPAC Meeting: Use of MDCK Cells for the Manufacture of Inactivated Influenza Vaccines<sup>3</sup>

#### **ii. International post-marketing experience with the same product**

As noted above, there are no non-study post-marketing reports for Optaflu. Non-study distribution is limited to ----(b)(4)----- sold in Germany in 2008.

## **3. Pharmacovigilance Plan review**

### **a. Clinical safety database**

The clinical safety of Optaflu is based upon 7 studies. In total, 6473 study subjects 18 to 64 years of age received 6817 doses of Optaflu. In addition, 779 study subjects  $\geq 65$  years of age received 997 doses of Optaflu as part of the clinical trials. Some studies also enrolled pediatric patients. A total of 1599 children 3 to 8 years of age and 652 adolescents 9 to 17 years of age also received Optaflu. (BLA 2.7.4 Summary of Clinical Safety, p11) In each of the 7 studies, cTIV was compared to an egg-derived influenza vaccine (eTIV). In 6 of these studies, this was Agriflu (Novartis). In one study, V58P5, the comparator vaccine was Fluvirin (Novartis). (BLA 2.7.4 Summary of Clinical Safety, p10) The eTIV population is composed of 5154 adults 18 to 64 years of age and 547 adults  $\geq 65$  years of age. (BLA 2.7.4 Summary of Clinical Safety, p26)

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<sup>2</sup> Available at: <http://www.fda.gov/ohrms/dockets/ac/05/minutes/2005-4188m1.pdf>

<sup>3</sup> Available at: [http://www.fda.gov/ohrms/dockets/ac/05/briefing/5-4188B1\\_3.htm](http://www.fda.gov/ohrms/dockets/ac/05/briefing/5-4188B1_3.htm)

While specifics in the study protocols differed, solicited AEs which occurred within 1 week of vaccination were recorded on diary cards. The particular AEs were selected based upon known AEs with other inactivated influenza vaccines. Subjects reported unsolicited AEs to the study investigator if they occurred within 1 week (studies V58P5 and V58P13) or 3 weeks (all other studies). For 5 of the studies, selected AEs were recorded for up to 6 months following vaccination. (BLA 2.7.4 Integrated Summary of Safety, p33) This section will address solicited AEs, unsolicited AEs, deaths, and serious adverse events observed in the pooled safety data.

### **Solicited Adverse Events (Adults and Older Adults)**

In the pooled safety data, a small, statistically significant increase in the rate of local reactions on days 1- 7 among Optaflu recipients aged 18-64 years was identified, compared to eTIV recipients (RR = 1.10, 95% CI: 1.04 – 1.15). The most frequently reported local reactions in the 18-64 year old age group were pain at the injection site, erythema, and induration. An imbalance was noted between the Optaflu and control groups for injection site pain rated “mild” in intensity (cTIV 24% vs. eTIV 21%). No similar imbalance was noted for moderate and severe injection site pain (3% and <1%, respectively). (BLA 2.7.4, p37-8) The risk of systemic reactions was not increased in this age group. In addition, the risk of systemic or local reactions was not increased in adults ≥65 years of age. This is shown in Table 2.1.1.1-2 from the BLA.

**Table 2.1.1.1-2 Solicited AEs in the Pooled Safety Population (Days 1 - 7)**  
**Pooled Exposed Safety Population\***

Type of Reaction	Adults 18 - 64 Years			Adults ≥65 Years		
	Percentages cTIV <sup>a</sup> N=6138	Percentages eTIV-a/f <sup>b</sup> N=5154	Weighted Risk Ratio (95% CI)	Percentages cTIV N=572	Percentages eTIV-a N=547	Weighted Risk Ratio (95% CI)
Any	51	49	1.06 (1.02 - 1.10)	35	34	0.99 (0.85 – 1.16)
Local	38	36	1.10 (1.04 - 1.15)	22	19	1.07 (0.86 – 1.35)
Systemic	29	29	1.03 (0.97 - 1.09)	22	22	0.97 (0.78 – 1.21)
Other <sup>d</sup>	10	12	0.94 (0.85 - 1.04)	6	5	1.04 (0.64 – 1.68)

\*excluding study V58P4E1 and the placebo group of study V58P13, <sup>a</sup>cTIV = Cell cultured-derived influenza vaccine;

<sup>b</sup>eTIV-a/f = Egg-derived influenza vaccine; <sup>c</sup>CI = Confidence interval; <sup>d</sup>Other = Stayed home due to a reaction and/or used analgesic or antipyretic medication.

(From BLA 2.7.4, p37)

The most frequently reported systemic reactions following cTIV for adults 18 – 64 years of age were headache (16%), Fatigue (12%), and myalgia (11%). Incidences in the eTIV group were similar. (BLA 2.7.4, p39) For adults ≥ 65 years of age, the most common systemic reactions were fatigue (11%), headache

(10%), and malaise (10%). The incidences of these adverse events in the eTIV group was slightly higher (13%, 11%, and 11%). Fever was reported by <1% of subjects in the cTIV group. (BLA 2.7.4, p44-5)

In order to evaluate reactogenicity in a subsequent influenza season, an extension study was performed. Subjects from study V58P4 could receive a second dose of influenza vaccine in the following flu season. Subjects were enrolled at a 1:1 ratio to receive either cTIV or eTIV (irrespective of which vaccine the subject received in the prior season). Thus, there were 4 groups in the second season, each having received either eTIV or cTIV in the first season and either eTIV or cTIV in the second season. For the 18 - 64 year age group, the percentages of subjects who reported local or system solicited adverse events in the 7 days following vaccination was lower in year 2 vs. year 1. In addition, the year 2 percentages were similar across all 4 groups. See Table 2.1.1.2-2 below.

**Overview of Solicited AEs (Days 1 – 7) - Adults 18 - 64 Years who Received Two Doses of Vaccine, 1 Year Apart**

Type of Reaction	Percentages of Subjects					
	V58P4		V58P4E1			
	cTIV <sup>a</sup> N=821	eTIV-a <sup>b</sup> N=841	cTIV/cTIV N=344	cTIV/eTIV-a N=333	eTIV-a/cTIV N=335	eTIV-a/eTIV-a N=329
Any	39	38	31	31	37	31
Local	31	28	26	26	30	27
Systemic	22	22	15	16	17	15
Other <sup>c</sup>	8	7	5	3	5	5

<sup>a</sup>cTIV = Cell culture-derived influenza vaccine; <sup>b</sup>eTIV-a = Egg-derived influenza vaccine; <sup>c</sup>Other = Stayed home due to a reaction and/or used analgesic or antipyretic medication.

(BLA 2.7.4, p47)

When severe systemic reactions were examined, there was a significant increase in the cTIV/cTIV group vs. other groups. However, all reactions resolved by 7 days after vaccination, no reaction was rated as severe for >3 days, and no common pattern was identified.

**Table 2.1.1.2-4 Overview of Severe Reactogenicity (Days 1 – 7) in Adults 18 – 64 Years - Study V58P4E1**

Type of Severe Reaction	Number (Percentages) of Subjects							
	V58P4E1			V58P4E1				
	cTIV <sup>a</sup> N=679	eTIV-a <sup>b</sup> N=662	P-Value <sup>c</sup>	cTIV/ cTIV N=344	cTIV/ eTIV-a N=333	eTIV-a/ cTIV N=335	eTIV-a/ eTIV-a N=329	P-Value <sup>c, d</sup>
Any Reaction	10 (1)	3 (<1)	0.57	7 (2)	2 (<1)	3 (<1)	1 (<1)	0.11
Local	3 (<1)	2 (<1)	1.0	2 (<1)	1 (<1)	1 (<1)	1 (<1)	0.91
Systemic	8 (1)	1 (<1)	0.039*	6 (2)	1 (<1)	2 (<1)	0	0.031*

<sup>a</sup>cTIV = Cell culture-derived influenza vaccine; <sup>b</sup>eTIV-a = Egg-derived influenza vaccine; <sup>c</sup>P-value for

categorical variables computed by the chi-square test if  $\leq 20\%$  of the cells have expected cell counts less than 5, or by Fisher's Exact test if  $>20\%$  of the cells have expected cell counts less than 5; <sup>d</sup> overall treatment effect; \*  $P < 0.05$ .

(BLA 2.7.4, p49)

For adults  $\geq 65$  years of age, the rates of local and systemic reactions were less in year 2 vs. year 1. In addition, the percentages of patients experiencing local and systemic adverse reactions were similar between the 4 groups. Severe systemic reactions were reported in  $<1\%$  of patients and there was no imbalance between the groups. (BLA 2.7.4, p51-4)

In summary, although certain minor differences between study groups were observed, the overall reactogenicity of the cTIV is not substantially different than eTIV. The most clinically significant difference was a small but statistically significant increase in injection site reactions following cTIV for patients in the 18 – 64 year age group.

#### **Unsolicited Adverse Events (Adults and Older Adults)**

For the 18 – 64 year age group, the rate of unsolicited adverse events was similar in the cTIV and eTIV groups (9% vs. 10%). No single unsolicited AE was reported by more than 2% of subjects in the 7 days following vaccination. Unsolicited AEs reported by  $\geq 1\%$  of the pooled safety population included oropharyngeal pain, cough, headache, malaise, rhinitis, fatigue, and injection site hemorrhage. With the exception of injection site reactions, these AEs are common in the general population and would be expected to occur. Rates of individual AEs between the cTIV and eTIV groups were not significantly different. There were no differences in the intensity of unsolicited AEs between the cTIV and eTIV groups and most unsolicited AEs were mild in intensity. (BLA 2.7.4, p55-8)

Results in the  $\geq 65$  years of age population were similar. Unsolicited AES were followed for 3 weeks in all patients  $\geq 65$  years. The percentage of patients experiencing unsolicited AEs was similar in the cTIV and eTIV groups (8% vs. 7%). Also,  $\leq 1\%$  of both the cTIV and eTIV groups reported any single unsolicited AE. Most possibly/probably related AEs were mild in intensity and there were no severe reactions reported. (BLA 2.7.4, p61-4)

#### **Deaths (Adults and Older Adults)**

There were 13 deaths in the 7 studies. The vaccine groups for the 13 deaths were as follows: 7 in cTIV, 5 in the eTIV, 1 placebo. All deaths were judged by the study investigators to be unrelated to vaccination. Of the 13 deaths, 12 were in the follow-up period of 3 weeks to 6 months post-vaccination. There was no predominant COD identified. Of the 7 cTIV deaths, 6 were in adults 18 – 64 years of age and 1 was in an adult  $\geq 65$  years of age. (BLA 2.7.4, p65-6) A complete listing of each death is provided in the table below. (Adapted from BLA 2.7.4, Table 2.2.2-1, p67)

Study	Subject No.	Age (years)	Vaccine Group	Primary Cause of Death	Study Day	Relatedness
<b>Adults 18 - 64 Years</b>						
V58P4E1	01/0128	57	cTIV	Suicide by drug intoxication (imipramine and levomepromazine)	a	none
V58P9	01/0203	58	cTIV	Suffocation due to compression of neck	50	none
V58P13	09/281	35	cTIV	Dyspnea	153	none
V58P13	17/299	37	eTIV-a	Homicide	99	none
V58P13	31/320	31	Placebo	Cerebral haemorrhage	33	none
V58P13	35/169	38	cTIV	Unknown	75	none
<b>Adults ≥65 Years</b>						
V58P4	01/2259	73	eTIV-a	Hypertension leading to a cerebrovascular accident	43	none
V58P4	03/2147	75	cTIV	Intoxication carbon monoxide	25	none
V58P4	04/2009	77	eTIV-a	Adenocarcinoma of right lung	189	none
V58P4E1	01/2152	74	cTIV	Acute myocardial infarction	61	none
V58P4E1	01/2221	77	eTIV-a	Acute pancreatitis with diffuse peritonitis, pancreatic cyst and intestinal occlusion complicated by massive bleeding from digestive tube	120	none
V58P4E1	01/2554	77	eTIV-a	Cerebral hemorrhage	134	none
V58P4E1	05/2148	88	cTIV	Sudden cardiac death	35	none

<sup>a</sup>Occurred October 2005, precise date not provided

Of the 7 cTIV group deaths, two are clearly unrelated to vaccination: suicide and carbon monoxide poisoning. In addition, a single death from an acute MI in a 74 year old 61 days after vaccination is also unrelated, as any cardiac effects would most likely results from acute stress (minutes) and not days to months s/p vaccination.

Examining the other cTIV group deaths revealed no evidence of relatedness. Subject 01/0203 is listed as dying from “compression of the neck” or “injury

asphyxiation.” (BLA 5.3.5.1 V58P9 Final Clinical Study Report, p103) Although no additional details are provided, the description of an “injury” and the occurrence of the event 50 days after vaccination indicate that this death is also unrelated. Subject 09/281 is described as dying from “dyspnea” 153 days s/p vaccination. According to the study report, the subject was a 35 year old female with a history of obesity and hypertension. She was hospitalized on day 149 s/p vaccination for severe dyspnea and died on day 153. COD was listed as dyspnea. (BLA 5.3.5.1 V58P13 Final Clinical Study Report, p111) Given the patient’s risk factors for cardiovascular and/or lung disease and the long latency between vaccination and the onset of her fatal illness, this death would also seem to be unrelated to cTIV. Subject 35/169 is listed as having an unknown COD in the above table. Details in the Final Clinical Study Report are sparse, but it is known that the subject was a 38 year old male with a history of hypertension and was being treated with 3 anti-hypertensive medications. On day 12 s/p vaccination, he was hospitalized for LOC and discharged the following day. He died on day 75 of an unknown cause. (BLA 5.3.5.1 V58P13 Final Clinical Study Report, p112) While more details would be helpful in assessing this patient’s death, the 1 day hospitalization on day 12 makes a cerebrovascular accident unlikely, particularly as the patient is described as “recovered.” Given the multiple anti-hypertensives, his LOC could have been related to his hypertension or to adverse effects of the medications. In addition, the 75 day latency makes any relatedness to cTIV very unlikely. The final cTIV death is described as a sudden cardiac death in an 88 year old patient 35 days s/p vaccination. No additional deaths are provided in the study report. Given the patient’s advanced age and the 35 days between vaccination and death, there is no evidence of relatedness.

In conclusion, there was no imbalance between the number of deaths in the cTIV and eTIV groups. Analysis of each cTIV death did not reveal any indication of relatedness to vaccination. While some details are lacking, the long latencies between vaccination and death and the available facts support the study investigators’ conclusion that all c TIV deaths were unrelated.

#### **Serious Adverse Events (Adults and Older Adults)**

For the entire study duration (3 weeks for 2 studies and 6 months for 5 other studies), there were 270 serious adverse events experienced by study subjects (in all groups). None were judged to be product related. In the 18 to 64 age group, there were 85 cTIV subjects (1%) and 56 eTIV subjects (1%) who experienced serious AEs. Reviewing the coded SOC and PTs, there were no imbalances between the 2 groups. (BLA 2.7.4, p69-77)

For the  $\geq 65$  years of age group, 4 subjects in the cTIV group ( $<1\%$ ) and 4 subjects in the eTIV group ( $<1\%$ ) experienced serious AEs on days 1-22. For the 5 studies with 6 month follow-up, 33 adults  $\geq 65$  years of age had serious AEs in cTIV group (3%) while 40 subjects in the eTIV group (4%) experienced serious AEs. Examining the coded SOC and PTs, there were no imbalances between the 2 groups. (BLA 2.7.4, p88-94)



### **Use in Pregnancy and Lactation**

Although clinical studies were not designed to evaluate the safety of cTIV in pregnant and lactating women, and birth control was an entry criterion in the studies, a total of 60 women became pregnant within the 6 month follow-up period. Study groups for the pregnant subjects and pregnancy outcomes were as follows:

#### **Pregnancy Outcomes and Study Group for 60 Patients who became Pregnant during Follow-up Period for cTIV Studies**

Pregnancy Outcome	cTIV	eTIV	Placebo	Total
Normal/ no congenital anomalies	12	17	13	42
Spontaneous Abortion	2	2	1	5
Ectopic Pregnancy	1	1	0	2
Unknown/lost to f/u	3	4	4	11
Totals	18	24	18	60

(BLA 2.7.4, p.113)

While the number of patients is small and a significant number were lost to follow-up, it is reassuring that the no congenital anomalies were observed. In addition, 80% (12 of 15) pregnancies with known outcome in the cTIV group resulted in the birth of healthy newborns. However, the numbers of pregnancies and outcomes is too small to draw any firm conclusions at this time. In terms of pharmacovigilance, information regarding pregnancy and lactation should still be regarded as “missing information.”

### **Pediatric Patients**

Pediatric patients were divided into children 3 to 8 years of age and adolescents 9 to 17 years of age. A total of 1599 children 3 to 8 years of age received cTIV and 1013 received eTIV. Similar percentages of the cTIV and eTIV recipients reported local and systemic reactions. Most reactions were mild to moderate. The most common local reaction was pain (28% cTIV and 25% eTIV) and the most common systemic reaction was fatigue (10% cTIV and 12% eTIV). There were no related serious AEs and no deaths among children 3 to 8 years of age.

A total of 652 adolescents received cTIV and 315 received eTIV. Again, the proportion of patients in each group reporting local or systemic AEs was similar. Most reactions were mild to moderate in intensity. The most common local reaction was pain (24% cTIV and 38% eTIV) and the most common systemic reaction was myalgia (15% in both cTIV and eTIV). There were no related, serious AEs and no deaths among adolescent study participants. (BLA 2.7.4, p136-40)

b. Safety concerns

**i. Important identified safety issues**

None. (BLA 1.16, p15)

Although the sponsor cites “anaphylactic reaction” as a potential safety issue, the label states “Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following the administration of the vaccine.” (BLA 1.14.1.2 Annotated Package Insert, p4-5) The sponsor’s categorization of anaphylactic reaction as a potential risk is based upon 1 case of anaphylaxis (characterized by angioedema) seen in the clinical trials. This episode occurred 35 days s/p vaccination and was judged to be unrelated to vaccination. (BLA 1.16, p15-7)

**ii. Important potential safety issues**

The sponsor has identified 9 potential safety issues, all of which have been reported following other influenza vaccines. These are neuritis, convulsion, anaphylactic reaction, encephalitis, vasculitis, GBS, demyelination disorders, Bell’s palsy, and immune thrombocytopenia. Only 2 of these potential safety issues were observed during the cTIV trials: 3 patients experienced seizure (earliest onset was 72d s/p vaccination) and 1 patient experienced anaphylaxis. Seven (7) patients reported urticaria and 1 reported angioedema (35d s/p vaccination). No cases of neuritis, encephalitis, vasculitis, GBS, demyelination, Bell’s palsy, or immune thrombocytopenia were observed during the pre-licensure studies. (BLA 1.16, p15-7) However, these events can be very rare (GBS) and pre-licensure studies may be of insufficient size to detect an increase in risk. The sponsor proposes routine pharmacovigilance activities for these potential safety issues. Given the lack of any signal in the studies and the extremely large populations required to detect small increases in the risk of rare adverse events, routine pharmacovigilance is acceptable.

**iii. Important missing information**

There are 4 areas of important missing information: use in infants and toddlers, safety in subjects with underlying diseases, safety in immunocompromised subjects, and the use of cTIV in pregnant and lactating women. (BLA 1.1.6, p40)

The use of cTIV in infants and toddlers is being evaluated in Study V58P16. This study is designed to evaluate the safety and immunogenicity of cTIV in subjects 6 to 35 months of age. Patients will be stratified into 2 groups: 6-23 months and 24-35 months of age. Within each group, subjects will be randomized to receive either a double dose, a full dose, or 2 half-doses (given 4-8 weeks apart). The plan is to enroll approximately 420 children. An additional 60 children will be enrolled as a comparator group who will receive a currently licensed influenza vaccine. Immunogenicity will be measured 3 weeks s/p vaccination.

Solicited local and systemic adverse events will be recorded for 1 week. Unsolicited AE will be monitored for 3 weeks and any AE that is serious, results in study withdrawal, or the new onset of a chronic disease will be collected for 6 months. (BLA 1.1.6, p37).

The use of cTIV in patients with underlying medical conditions was evaluated in Study V58P14, a multi-center, active-controlled study conducted in Germany in 2007-08.<sup>4</sup> A total of 1398 adults (1002 received cTIV and 396 received eTIV) were enrolled in the 2007-08 influenza season. However, the study was prematurely terminated in 2010, due to unavailability of the vaccine. The original plan was to enroll approximately 6000 patients. Solicited AEs were recorded for 1 week following vaccination. In addition, unsolicited AEs were recorded for 3 weeks. Any serious AE, an AE which required a physician visit, any AE reported as the worsening of an underlying medical condition or the new onset of a medical condition, and AEs that resulted in study withdrawal were recorded for 6 months. Study results are not currently available. (BLA 1.1.6, p38) While this study did not enroll as many patients as planned, the collected data could provide useful information. These results should be analyzed and the study results provided to the FDA.

The safety of cTIV in immunocompromised subjects is unknown. The sponsor proposes routine pharmacovigilance. Given that cTIV is not a live virus vaccine, there are no particular safety concerns specific to this population and routine PV is acceptable.

The final area of important missing information is the use of cTIV in pregnant women. The sponsor proposes routine pharmacovigilance. Given the reassuring data (although limited by small numbers) above, routine PV is acceptable.

c. Sponsor's proposed actions

i. Enhanced PV activities proposed by the sponsor

To evaluate the use of cTIV in children 6-35 months, the sponsor proposes to conduct Study V58P16, as described in section 3b.iii. above. To evaluate the use of cTIV in subjects with underlying disease, the sponsor proposes Study V58P14. This study was conducted in Germany in 2007-08, but results have not been made available at this time.

4. Postlicensure Safety Review

a. Worldwide

i. Non-U.S. data

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<sup>4</sup> The sponsor does not specify particular underlying conditions with reference to V58P16. However, underlying chronic conditions are described as "conditions affecting the circulatory and respiratory systems and diabetes mellitus" in a separate section of the BLA. (BLA 2.5 Clinical Overview, p23)

The sponsor states that (b)(4)-- doses of cTIV were sold in Germany in Q1 2008. According to the Risk Management Plan, “no confirmed spontaneous cases” of adverse events following cTIV have been received. (BLA 1.1.6, p9)

b. U.S.

i. There is no postlicensure data for the U.S. Novartis cTIV has never been licensed in the U.S

5. Integrated Safety Assessment

**a. Description of important safety issues identified by the reviewer from any source that do not trigger a PMR or REMS**

There were no important safety issues identified in the 7 clinical trials. The sponsor has identified 9 potential safety issues, which have been observed with other influenza vaccines. These are described in section 3b.ii. above. The sponsor identified 4 areas of important missing information. These are use in infants and toddlers, use in patients with underlying conditions, use in immunocompromised patients, and use in pregnant women. The sponsor has proposed to analyze data gathered from a study in Germany in 2007-08 (V58P14) to assess the use of cTIV in patients with underlying medical conditions. The sponsor has also proposed a study (V58P16) to evaluate the immunogenicity, dosing, and safety of cTIV in infants and toddlers. Please see section 3b.iii. above for additional details.

**b. Description of any signals identified that trigger a PMR or REMS**

None.

6. Recommendations

**a. Routine pharmacovigilance**

The sponsor has proposed routine pharmacovigilance to monitor the potential safety issues described in 3b.ii. above. These are adverse events which have been previously associated with other influenza vaccinations (seizures and GBS after eTIV and Bell’s palsy after a European licensed intranasal TIV) or are theoretical safety concerns by virtue of being immune mediated conditions (encephalitis, vasculitis, demyelinating disorders, ITP). There were no safety signals for these potential safety issues in the clinical trials. Routine pharmacovigilance is an acceptable strategy.

**b. Outstanding studies**

The use of cTIV in patients with underlying medical issues was studied 1398 adults as part of Study V58P14. The Risk Management Plan states the results of this study are not yet available. The data from this study needs to be analyzed and the report provided to the FDA. This study may provide important information about the use of cTIV in a population at increased risk of influenza complications.

The proposed age indication for cTIV is for persons >18 years of age. A total of 2251 children received cTIV during the clinical trials. Children under 3 years of age were not studied. Study V58P16 has been proposed to assess the immunogenicity and safety of cTIV in children 6-35 months of age. While this information is not needed for the proposed age indication, pediatric data would be needed before a pediatric indication could be considered.