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A prospective observational safety study on MF59® adjuvanted cell culture-derived vaccine, Celtura® during the A/H1N1 (2009) influenza pandemic

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ABSTRACT

Background: The present study was a prospective observational study to evaluate the safety profile of Celtura®, a monovalent, cell culture-derived, inactivated subunit influenza vaccine prepared from A/California/07/2009(H1N1) with the adjuvant MF59®. Subjects were enrolled prospectively during the H1N1 2009 influenza pandemic at medical centres in Colombia, Chile, Switzerland, and Germany during the period December 2009 to June 2010.
Methods: Subjects ages 18 and older were followed for the occurrence of adverse events (AEs) for six months after vaccination. Adverse events of special interest (AESIs) were neuritis, convulsion (seizure), anaphylaxis, encephalitis, vasculitis, Guillain-Barre syndrome, demyelinating conditions, Bell's palsy, and laboratory-confirmed vaccination failure.
Results: Overall, 7348 AEs were reported in 2296 of 3989 enrolled subjects (57.6%). Only two AEs were considered related to injection site reactions. No laboratory-confirmed cases of influenza were reported. There were 108 medically confirmed serious adverse events (SAEs) reported among 73 subjects with 6 such SAEs described as possibly or probably related to vaccination. Three fatal cases were reported and assessed as not related to vaccination. Two AESIs classified as convulsion were reported and assessed as not related to vaccination. Both AESIs occurred well outside the pre-specified 7 day risk window representing the likely timeframe of the occurrence of seizure following vaccination.
Conclusions: The results of this study support the overall good safety profile of MF59 adjuvanted cell culture-derived influenza vaccine as administered in adults during the 2009–2010 H1N1 influenza pandemic. No concern is raised regarding the occurrence of AESIs.

1. Introduction

Post-licensure vaccine surveillance studies are essential for establishing the safety and adverse event (AE) profiles of new vaccines by identifying rare AEs (occurring with cumulative incidence of 0.01–0.1% as defined by the Council for International Organizations of Medical Sciences) [1] not detected during pre-licensure studies. These studies may distinguish true vaccine reactions from coincidental unrelated events and help to maintain public confidence in immunizations.

The study vaccine, Celtura®, is a monovalent, cell culture-derived, inactivated subunit vaccine prepared from A/California/07/2009(H1N1)v with the adjuvant MF59®. The production of the viral antigen components is based on a validated cell culture line rather than traditional chicken eggs. This technology has been licensed in Europe for the production of the seasonal

Abbreviations: AE, adverse event; AESI, adverse event of special interest; CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; HLT, High Level Term; PT, Preferred Term; SAE, serious adverse event; SOC, System Organ Class; WHO, World Health Organization.

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influenza vaccine, Optaflu® [2,3]. Both vaccines proved to be well tolerated and demonstrated a comparable immunogenicity and safety as egg-derived subunit vaccines [4–6]. MF59 is a widely used adjuvant in both seasonal and pandemic influenza vaccines with a good safety profile in post marketing surveillance [7–10].

This study was conducted in Europe and South America following the successive implementation of local vaccination campaigns and was designed to meet post marketing commitments for Celtura as published by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) [11]. Adverse events of special interest (AESIs) as defined by the CHMP guidelines were neuritis, convulsion (seizure), anaphylaxis, encephalitis, vasculitis, Guillain-Barre syndrome, demyelinating conditions, Bell's palsy, and laboratory-confirmed vaccination failure.

2. Methods

2.1. Study design

The primary objective of this study was to assess the safety of Celtura by estimating the incidence of reported AEs, serious adverse events (SAEs), and AESIs requiring medical attention and characterizing the incidence of any AE in specific age groups following active surveillance of vaccinated subjects [12]. The secondary objective was to assess the occurrence of laboratory-confirmed influenza A/H1N1 (2009) infection and influenza-like illness (ILI) following vaccination.

This prospective observational study was conducted at medical centres in Colombia, Chile, Switzerland, and Germany in compliance with European Union Guidelines on Pharmacovigilance of Medicinal Products for Human Use and the World Health Organization (WHO) Pandemic Influenza Preparedness and Response guidance [13,14]. Subjects were enrolled at time of first or second dose of Celtura vaccination between December 2009 to June 2010. Subjects were followed for occurrence of AEs for six months if they received a single dose of vaccine or seven months if they received two doses of vaccine. Serious adverse events and AESIs were reviewed by a study medical monitor and confirmed against primary medical records or with the treating physician. The study protocol and informed consent documents were approved by local Ethics Committees as required for each site (ClinicalTrials.gov/NCT01037855).

2.2. Study population

Eligibility of subjects was in accordance with the product label in each country. Decision on vaccination was determined by the treating physician and the subject independently from the study protocol. Subjects received a single vaccination at enrolment and provided informed consent prior to vaccine administration to participate in study follow-up. Receipt of any prior H1N1 vaccination other than Celtura was the sole exclusion criterion.

2.3. Sample size

Sample size was calculated based on the CHMP recommendation for design of a pandemic influenza vaccine safety study of 9000 subjects with the following number of subjects per age group: 6–23 months ($n = 500$), 2–8 years ($n = 500$), 9–17 years ($n = 3000$), 18–44 years ($n = 1500$), 45–60 years ($n = 1500$), and >60 years ($n = 2000$) [11]. Only 39 subjects were under the age of 18 in this study, well below the recommended sample size of 4000 subjects in this age group. Therefore, subjects <18 are excluded from statistical analyses as it is impossible to detect rare AEs in such a small population.

2.4. Data collection

Baseline data were collected from both physician and subject on the day of enrolment. Information collected included demographics, vital signs, details of Celtura vaccine administration, and medical history (allergic reactions to prior vaccines, pregnancy status, concomitant medications, concurrent vaccinations). Immediate surveillance for any acute reactions which could be related to the vaccine or administration procedure was recorded by the physician. Details of any AEs that occurred while the subject was on-site since first vaccine dose were additionally recorded.

For most subjects, telephone surveys were scheduled seven days following vaccine dose and monthly thereafter for six months. Alternatively, mail or internet questionnaires were available to reach all subjects. The questionnaires included questions about possible AEs/SAEs for which the subject sought medical attention or was hospitalized, possible ILI, pregnancy status, and symptoms consistent with possible AESIs. In addition to the information provided directly by subjects, the treating physician reported potential AEs/SAEs identified through evaluation of the subject or reported to them by the subject during follow-up.

2.5. Medical monitoring and confirmation of ILI, SAEs, and AESIs

Reported AEs indicating fever and cough or sore throat associated with any of the following symptoms: body aches, chills, headache and runny/stuffy nose were categorized as ILI. For subjects who reported having received nasal swab testing, confirmation of the testing and results were requested from the physician.

Serious adverse events were defined following the International Conference on Harmonisation Good Clinical Practice guidelines [15]. Medical monitoring was triggered by the report of a potential SAE by study staff and reviewed within 24 h to determine the seriousness of the event. All SAEs were confirmed through direct follow-up with the treating physician and/or review of medical records.

Reported suspected AESIs were reviewed by a medical monitor in accordance with the Brighton Collaboration case definition for anaphylaxis, seizure, Guillain-Barré syndrome and encephalitis or to clinical definitions for Bell's palsy, demyelinating conditions, neuritis, vasculitis, and laboratory-confirmed vaccination failure that were developed for purposes of the study. Vaccination failure followed the clinical and laboratory definitions outlined by the Council for International Organizations of Medical Sciences/WHO Working Group on Vaccine Pharmacovigilance [16,17]. Events confirmed as SAEs or AESIs were reported as medically confirmed.

In addition, records of subjects with multiple AEs where one was reported by the subject and one by the treating physician were reviewed by a medical monitor to identify duplicate AE reporting.

2.6. Analysis of AEs

All AEs were coded using MedDRA (version 12) and are presented by System Organ Class (SOC), High Level Term (HLT) and Preferred Term (PT). Coding was reviewed by a medically trained reviewer. Frequencies and cumulative incidence of all AEs, SAEs, and AESIs following vaccination were reported for specified follow-up intervals.

Cumulative incidence was computed as the proportion of subjects who reported an AE following vaccination among all subjects who completed at least the number of days of follow-up specified for each interval including the full study period. Ninety-five percent confidence intervals for cumulative incidence were

Table 1
Counts of enrolled subjects vaccinated with Celtura by age and gender.[a]

Gender	Age-groups in years[b]	Colombia *N* (%)	Chile *N* (%)	Switzerland/Germany *N* (%)	Total *N* (%)
Female	18–44 years	1394 (37.5)	87 (45.3)	44 (53.0)	1525 (38.2)
	45–60 years	661 (17.8)	31 (16.1)	1 (1.2)	693 (17.4)
	>60 years	258 (6.9)	5 (2.6)	2 (2.4)	265 (6.6)
Male	18–44 years	690 (18.6)	44 (22.9)	36 (43.4)	770 (19.3)
	45–60 years	501 (13.5)	22 (11.5)	0 (0.0)	523 (13.1)
	>60 years	210 (5.7)	3 (1.6)	0 (0.0)	213 (5.3)
	Totals	3714 (100.0)	192 (100.0)	83 (100.0)	3989 (100.0)

[a] Subjects were vaccinated in Colombia, Chile, Switzerland, and Germany with one or two doses of Celtura.
[b] Integer age was calculated on first vaccination date.

computed to estimate statistical precision of the risk estimate using the Clopper-Pearson method [18,19].

2.7. Signal detection

In order to compare observed rates of AESIs with expected rates based on background incidence rates reported in the literature, risk windows, defined as the time period in days following vaccination during which a reported AESI may be assumed to be related to vaccination, were defined for each event type [16,20–39]. Counts of AESIs that occurred within the pre-specified risk window were compared against expected values using sequential testing methods including the maxSPRT test developed by Kulldorff [40].

3. Results

3.1. Counts and characteristics of enrolled subjects

There were 3989 subjects enrolled in Colombia, Chile, Switzerland, and Germany (Table 1). The ages for enrolled subjects ranged from 18 to 92 years (mean 41 years, median 39 years). All subjects received only one dose of vaccine. There were 2483 female subjects (62.2%) and 1506 male subjects (37.8%) with 57.5% between the ages of 18–44 years. One subject reported being pregnant at enrolment and 44 additional subjects reported pregnancy during follow-up.

Risk categories for subjects reported at baseline included prior adverse reactions to vaccines, chronic health conditions, immunodeficiency, and pregnancy at enrolment. Overall, 77 subjects (1.9%) reported at least one prior adverse reaction to vaccines. Cardiovascular disorders, diabetes, and asthma were present in 501 (12.6%), 135 (3.4%), and 96 (2.4%) subjects, respectively (Table 2).

Table 2
Overview of enrolled subjects vaccinated with Celtura by risk categories.

Risk category	Vaccinated subjects *n*[a]	(%)
Prior adverse reaction(s) to vaccines	77	(1.9)
Asthma	96	(2.4)
Chronic obstructive pulmonary disease (COPD)	38	(1.0)
Diabetes	135	(3.4)
Chronic neurological disease	26	(0.7)
Cardiovascular disorders	501	(12.6)
Immunodeficiency[b]	16	(0.4)
Pregnant at time of first vaccination	1	(0.0)

[a] Total number of vaccinated subjects in risk categories: 760.
[b] Immunodeficiency was not defined; case report forms asked 'Is the subject immunocompromised for any reason?'.

3.2. Study discontinuation and response rates

Sixty-seven subjects (1.7%) discontinued the study of which 59 subjects were lost to follow-up, 5 subjects withdrew from the study, and 3 subjects died. The overall response rate was 97.2% (3842 of 3951 subjects) at 180 days follow-up for all subjects.

3.3. Frequencies and rates of AEs

There were 7348 AEs for which 2296 of 3989 subjects (57.6%) sought medical attention. Of these, 727 AEs were medically confirmed. The most frequently reported AEs at the MedDRA SOC level were "General Disorders and Administration Site Conditions" [$n = 4198$, cumulative incidence 55.0% of subjects (CI 53.1–56.2)], "Respiratory Thoracic and Mediastinal Disorders" [$n = 1244$, cumulative incidence 12.0% of subjects (CI 10.9–12.9)], and "Infections and Infestations" [$n = 580$, cumulative incidence 12.0% of subjects (CI 11.0–13.0)] (Table 3).

The "General Disorders and Administration Site Conditions" SOC includes asthenic conditions, febrile disorders, feelings and sensations, general signs and symptoms of ILI, injection site reactions, oedema, and chest pain and discomfort. There were 2 AEs related to vaccine injection, one instance each of injection site swelling and injection site abscess.

The "Respiratory Thoracic and Mediastinal Disorders" SOC includes asthma, coughing and associated symptoms, nasal congestion, upper respiratory tract signs and symptoms, and oropharyngeal pain. The "Infections and Infestations" SOC includes influenza, ear infections, lower respiratory tract and lung infections, upper respiratory tract infections, and viral infections.

The most commonly reported AEs at the MedDRA PT level included ILI [53.0% (CI 51.7–54.8)], cough [9.8% (CI 8.9–10.7)], nasal congestion [9.3% (CI 8.4–10.3)], oropharyngeal pain [8.8% (CI 7.9–9.7)], and headache [8.6% (CI 7.8–9.5)]. All AEs with a cumulative incidence of 1.0% or greater are listed in Table 4. Table 5 shows the most common AEs at each SOC level stratified by age group.

There were 3112 instances of ILI reported as AEs among 2146 subjects (53.8%) with onset of ILI occurring 1–181 days following vaccination (mean 86.3 days, median 85.0 days). No subjects were identified as having received nasal swab testing, thus there were no confirmed cases of influenza.

Eleven AEs were reported among 3 subjects with concomitant seasonal influenza vaccine administered concurrently with Celtura. One subject reported two AEs, gastric ulcer and ulcer, both associated with a recurrent stomach complaint. The gastric ulcer was reported by the treating physician and determined to be an SAE not related to Celtura vaccination. The second subject reported an instance of ILI. The third subject reported one instance each of ear pain, pyrexia, chills, bronchitis, sinusitis, oropharyngeal pain, headache, and nasal congestion.

Table 3
All adverse events at the MedDRA SOC level.

AE SOC name	Medically confirmed (*n*)	Non-medically confirmed (*n*)	Total number (*n*)	Cumulative incidence (%[a] (CI[b]))
General disorders and administration site conditions	18	4180	4198	55.0% (53.1–56.2)
Respiratory thoracic and mediastinal disorders	22	1222	1244	12.0% (10.9–12.9)
Infections and infestations	449	131	580	12.0% (11.0–13.0)
Nervous system disorders	37	385	422	9.2% (8.3–10.1)
Musculoskeletal and connective tissue disorders	27	320	347	5.6% (4.9–6.3)
Gastrointestinal disorders	35	194	229	3.8% (3.2–4.4)
Ear and labyrinth disorders	11	96	107	2.5% (2.0–3.0)
Injury poisoning and procedural complications	38	17	55	0.8% (0.5–1.1)
Skin and subcutaneous tissue disorders	6	27	33	0.6% (0.4–0.9)
Eye disorders	11	8	19	0.4% (0.3–0.7)
Renal and urinary disorders	9	10	19	0.4% (0.2–0.6)
Reproductive system and breast disorders	10	9	19	0.4% (0.3–0.7)
Vascular disorders	12	3	15	0.4% (0.2–0.6)
Cardiac disorders	10	3	13	0.2% (0.1–0.4)
Metabolism and nutrition disorders	5	5	10	0.2% (0.1–0.4)
Hepatobiliary disorders	7	2	9	0.2% (0.1–0.4)
Psychiatric disorders	5	4	9	0.2% (0.1–0.4)
Pregnancy puerperium and perinatal conditions	6	0	6	0.1% (0.0–0.3)
Neoplasms benign malignant and unspecified	5	1	6	0.1% (0.0–0.3)
Immune system disorders	1	3	4	0.1% (0.0–0.3)
Endocrine disorders	3	0	3	0.1% (0.0–0.2)
Total	727	6621	7348	57.6% (56.0–59.1)

[a] Cumulative incidence of AEs was calculated as the proportion of subjects who reported the adverse event following first or second vaccination through end of follow-up among all enrolled subjects.
[b] CI: confidence interval.

There were 6 AEs reported by 5 women within the MedDRA SOC category "Pregnancy Puerperium and Perinatal Conditions." One instance of blighted ovum, determined to be an SAE, occurred in the woman pregnant at enrolment. The remaining 4 women were not pregnant at enrolment, but reported pregnancy-related conditions during follow-up, none related to vaccination. One woman reported a threatened abortion and retroplacental hematoma 179 days after last vaccination which resulted in a viable pregnancy and

Table 4
Most commonly reported adverse events at the MedDRA PT level.[a]

SOC HLT:PT name	Medically confirmed (*n*)	Non-medically confirmed (*n*)	Total number (*n*)	Cumulative incidence (%[b] (CI)[c])
Ear and labyrinth disorders				
Ear disorders: ear pain	0	91	91	2.1% (1.7–2.6)
Gastrointestinal disorders				
Nausea and vomiting symptoms: vomiting	1	83	84	2.1% (1.6–2.6)
Diarrhea (excl infective): diarrhea	4	75	79	1.9% (1.5–2.4)
General disorders and administration site conditions				
General signs and symptoms: influenza-like illness	14	3058	3072	53.0% (51.7–54.8)
Febrile disorders: pyrexia	1	336	337	8.0% (7.2–8.9)
Asthenic conditions: malaise	0	340	340	8.1% (7.3–9.0)
Feelings and sensations: chills	0	310	310	7.4% (6.6–8.3)
Asthenic conditions: fatigue	0	115	115	2.8% (2.3–3.4)
Infections and infestations				
Upper resp tract infections: nasopharyngitis	111	38	149	3.6% (3.1–4.2)
Upper resp tract infections: tonsillitis	60	11	71	1.8% (1.4–2.2)
Lower resp tract and lung infections: bronchitis	54	11	65	1.6% (1.2–2.0)
Influenza viral infections: influenza	33	7	40	1.0% (0.7–1.4)
Upper resp tract infections: laryngitis	31	9	40	1.0% (0.7–1.3)
Musculoskeletal and connective tissue disorders				
Muscle pains: myalgia	3	186	189	4.6% (3.9–5.3)
Joint related signs and symptoms: arthralgia	2	120	122	2.9% (2.4–3.5)
Nervous system disorder				
Headaches: headache	10	367	377	8.6% (7.8–9.5)
Respiratory thoracic and mediastinal disorders				
Coughing and associated symptoms: cough	2	423	425	9.8% (8.9–10.7)
Nasal congestion and inflam: nasal congestion	0	409	409	9.3% (8.4–10.3)
Upper resp tract signs and symp: oropharyngeal pain	1	376	377	8.8% (7.9–9.7)
Total AEs reported	727	6621	7348	57.6% (56.0–59.1)

[a] Table includes all AEs at the PT level with cumulative incidence of 1.0% or greater as well as the total number of AEs for all event types combined.
[b] Cumulative incidence of AEs was calculated as the proportion of subjects who reported the adverse event following first or second vaccination through end of follow-up among all enrolled subjects.
[c] CI: confidence interval.

Table 5
Common adverse events at the MedDRA SOC level within age categories.[a]

AE SOC level	Ages 18–44 years (*n*)	Ages 45–60 years (*n*)	Ages >60 years (*n*)
General disorders and administration site conditions	2483	1314	401
Respiratory thoracic mediastinal disorders	762	373	109
Infections and infestations	344	191	45
Nervous system disorders	265	129	28
Musculoskeletal and connective tissue disorders	203	116	28
Total AEs reported	4399	2288	661

[a] Table includes the top five most common AEs across all age groups at the SOC level as well as the total number of AEs for all event types combined per age group.

no hospitalization. Another woman reported a spontaneous abortion within one month of becoming pregnant, 50 days after last vaccination, and was not hospitalized. The remaining two women reported one instance of incomplete spontaneous abortion and one instance of ectopic pregnancy that were determined to be SAEs and are described further in the next section.

3.4. Frequencies and rates of SAEs

There were 108 SAEs, all medically confirmed, among 73 of 3989 subjects (Table 6). The most frequently reported SAEs were "Infections and Infestations" [$n = 37$, cumulative incidence 0.9% of subjects (CI 0.6–1.2)], "Injury Poisoning and Procedural Complications" [$n = 22$, cumulative incidence 0.3% of subjects (CI 0.2–0.5)], and "Nervous System Disorders" [$n = 10$, cumulative incidence 0.2% of subjects (CI 0.1–0.4)].

The "Infections and Infestations" SOC includes abdominal and gastrointestinal infections, bacterial infections, lower respiratory tract and lung infections, upper respiratory tract infections, and urinary tract infections. The "Injury Poisoning and Procedural Complications" SOC includes non-site specific injuries, spinal fractures and dislocations, and upper limb fractures and dislocations. The "Nervous System Disorders" SOC includes central nervous system hemorrhages and cerebrovascular accidents, disturbances in consciousness, paralysis/paresis, and seizures/seizure disorders.

Six SAEs in 4 subjects were reported by the treating physician as possibly or probably related to Celtura vaccination; one instance each of paraesthesia, pharyngitis, and laryngitis and 3 instances of bronchitis. Three subjects were reported with a fatal outcome with SAEs assessed as not related to vaccination (one case of road traffic accident, one case of acute myocardial infarction, and one case of cardio-respiratory arrest with sepsis, pneumonia and lower gastrointestinal hemorrhage).

Three SAEs were reported in 3 women at the MedDRA SOC level "Pregnancy Puerperium and Perinatal Conditions" and assessed as not related to vaccination by the treating physician. The 20 year old female pregnant at enrolment suffered from blighted ovum at 40 days after last vaccination. The other two SAEs were reported by two females who were not pregnant at enrolment, but reported pregnancy-related conditions during follow-up, none of which were related to vaccination; a 24 year old female reported an incomplete spontaneous abortion at153 days after last vaccination, and another 24 year old female was diagnosed with ectopic pregnancy 97 days after last vaccination.

3.5. Frequencies and rates of AESIs

Two AESIs, both instances of convulsion, were reported by two of the 3989 subjects. The events were considered SAEs as well as AESIs and were assessed as not related to vaccination. Onset of each event occurred 113 days and 138 days after last vaccination date, respectively. According to the Brighton Collaboration case definition for seizure, both episodes of convulsive seizure were classified as level 1 diagnostic certainty, as they included a witnessed sudden loss of consciousness with generalized tonic–clonic motor manifestations. Since neither convulsion occurred within the pre-specified risk window of 0–7 days following vaccination [41], no signal detection analyses were performed.

There were no AESIs reported in subjects with concurrent seasonal influenza vaccine or by subjects who were pregnant at enrolment.

3.6. Subjects <18 years of age

Thirty-nine subjects were under the age of 18 and excluded from statistical analyses. Twenty-two of the 39 subjects received two doses of vaccine. One instance of injection site urticarial was reported and no instances of narcolepsy or somnolence were reported. No SAEs or AESIs were reported in this age group.

4. Discussion

In April 2009 a new influenza A(H1N1) virus emerged, quickly spreading worldwide and prompting the WHO to declare an influenza pandemic. By the end of October 2009, there were more than 440,000 laboratory-confirmed cases reported to the WHO in approximately 200 countries [42]. By August 2010, the influenza pandemic moved to the post-pandemic period. It is estimated that 1–3 billion people became infected worldwide, but the actual number of influenza cases remains unknown as most were diagnosed clinically and not laboratory-confirmed. From a South American perspective, most countries were affected by the pandemic, and a high number of confirmed cases were reported (out of 9169 cases tested in Chile, 4037 were positive by PCR in 2009) despite laboratory testing not being routine procedure for influenza diagnosis [43–48].

Vaccination is considered one of the most effective tools in preventing the spread of influenza and mitigating the severity of illness and impact of disease [49]. In their final pharmacovigilance update, the EMA estimated 38.6 million people in Europe had been vaccinated with the three centrally authorized pandemic vaccines; Celvapan® (Baxter), a cell culture-based monovalent influenza vaccine, and two egg-derived adjuvant influenza vaccines, Focetria® (Novartis) and Pandemrix® (GlaxoSmithKline) [50,51]. Celtura gained local regulatory approval in Germany, Switzerland, Chile, and Peru. WHO prequalification was obtained in 2010 and more than 25.4 million doses of Celtura were distributed worldwide.

The safety of H1N1 pandemic vaccines was continually monitored during large clinical programs and most data have shown that the vaccines are well tolerated and have a similar profile to the corresponding seasonal vaccines in terms of safety and lack of severe AEs [48]. Epidemiologic studies carried out on one adjuvanted H1N1 pandemic vaccine in Finland indicated an increased risk of narcolepsy in children and adolescents compared to those that were unvaccinated [52]. However the relationship of H1N1 vaccination and narcolepsy is complex, as a study of 629 cases in China (86% among children) showed that narcolepsy incidence varies by month and calendar year (least frequent in November and

Table 6
All serious adverse events at the MedDRA SOC level.[a]

AE SOC name	Total number (*n*)	Cumulative incidence [%[b] (CI)[c]]	Possibly/probably related to vaccine (*n*)	Related to vaccine (*n*)	Related to fatal outcome (*n*)
Infections and infestations	37	0.9% (0.6–1.2)	5	0	2
Injury poisoning and procedural complications	22	0.3% (0.2–0.5)	0	0	1
Nervous system disorders	10	0.2% (0.1–0.4)	1	0	0
Cardiac disorders	8	0.2% (0.1–0.4)	0	0	2
Hepatobiliary disorders	6	0.2% (0.1–0.3)	0	0	0
Vascular disorders	4	0.1% (0.0–0.3)	0	0	0
Renal and urinary disorders	4	0.1% (0.0–0.3)	0	0	0
Gastrointestinal disorders	4	0.1% (0.0–0.3)	0	0	1
Respiratory thoracic and mediastinal disorders	3	0.1% (0.0–0.2)	0	0	0
Pregnancy puerperium and perinatal conditions	3	0.1% (0.0–0.2)	0	0	0
Neoplasms benign malignant and unspecified	3	0.1% (0.0–0.2)	0	0	0
Reproductive system and breast disorders	1	0.0% (0.0–0.1)	0	0	0
Musculoskeletal and connective tissue disorders	1	0.0% (0.0–0.1)	0	0	0
Metabolism and nutrition disorders	1	0.0% (0.0–0.1)	0	0	0
General disorders and administration site conditions	1	0.0% (0.0–0.1)	0	0	0
Total	108	1.8% (1.4–2.3)	6	0	6

[a] Table includes all SAEs at the SOC level.
[b] Cumulative incidence of SAEs was calculated as the proportion of subjects who reported the adverse event following first or second vaccination through end of follow-up among all enrolled subjects.
[c] CI: confidence interval.

most frequent in April) and appears to increase following influenza or other upper respiratory infections [53].

This observational study reflects the safety experience of 3989 enrolled subjects vaccinated with Celtura, including those in high risk groups. No instances of narcolepsy or somnolence were reported in the adult population. However, due to the limited number of children and adolescents enrolled ($n = 39$), the study data do not allow specific conclusions on the risk of narcolepsy or somnolence after vaccination with Celtura in these age groups.

One limitation of the study is that the overall target sample size of 9000 subjects set in the CHMP guidance was not reached despite expansion of the study into South America. Patient recruitment was in accordance with actual real-world prescribing practices, which are influenced by a number of potential factors including vaccine uptake, national recommendations, and organization of vaccination programs. In this study, low enrolment was mainly due to the late start of the vaccination campaign in Europe compared to the peak of the pandemic, the low vaccine uptake in Europe, and the late start of study recruitment during the pandemic in South America [54,55]. Very rare AEs that are seen only in large exposed populations are thus unlikely to be captured here. Nevertheless, the minimum sample size in the 18–44 age group of 1500 was met ($n = 2295$), and the minimum of 1500 was nearly met in the 45–60 age group ($n = 1216$).

One strength of this study is the overall response rate of 97.2% at the end of the study period with intensive medical monitoring in all subjects. A relatively high number of inter-current AEs ($n = 7348$) were reported in 2296 of 3989 subjects. Only two AEs were assessed as related to injection site reactions. It is likely that there was underreporting of mild injection site reactions. From the low number of related SAEs, it may be concluded that treating physicians and subjects did not frequently encounter severe injection site reactions. No evident increase in risk of SAEs or AESIs was observed.

Despite the high number of reports of ILI ($n = 3112$), no nasal swab testing was performed. It is not possible to determine whether a subject with signs and symptoms of ILI has true influenza in the absence of laboratory testing. Due to the nature of the MedDRA coding process, many AEs were coded as ILI when the subject presented with clinically confirmed respiratory symptoms. In addition, in some cases, physicians chose to classify the respiratory events as ILI. The large number of reports of ILI, approximately 1.5 respiratory illnesses per subject, was not unexpected given the follow-up period through winter months.

5. Conclusion

The results of this study confirm the good safety profile of MF59 adjuvanted cell culture-derived influenza vaccine Celtura as administered in adults during the H1N1 (2009) influenza pandemic. No concerns were raised regarding the occurrence of AESIs. The ability to assess effectiveness as measured by laboratory-confirmed influenza in this study is limited by the low frequency of testing for influenza in the observational setting.

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