Name and Address of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover, Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product Fluad®	Volume:	
Name of Active Ingredient: Vaccine composition: A/California/7/2009 (H1N1)-like virus A/Perth/16/2009 (H3N2)-like virus B/Brisbane/60/2008-like virus Adjuvans: MF59	Page:	

Title of Study:

A Phase II Study to Evaluate the Immunogenicity, Safety and Tolerability of a Seasonal Influenza Vaccine including H1N1 in Immunocompromised Adults Who Have Undergone Solid Organ Transplantation or Bone Marrow Transplantation and in Age-Matched Healthy Volunteers

Information about study protocol version(s):
Study protocol version no. 2.0, Nov. 05, 2010
Amendment 01 (13.01.2011): change in trial design: multicentre study instead of monocentre study, study protocol version no. 3.0 as of Dec. 28, 2010

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Publication (reference):

None at the time of the report, but a manuscript is in preparation.

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Studied period (years): (date of first enrolment) 24.11.2010 (date of last completed) 02.03.2012 Information about temporary halt(s) and premature termination of the trial: n/a	Phase of development: II

Objectives:

The trivalent adjuvanted seasonal influenza vaccine contains three virus strains. The H1N1 virus strain is of primary interest. Immune response to the vaccination is measured by HI-titers.

Primary objective:

The H1N1 vaccine (included in the trivalent influenza vaccine) when administered once in transplanted patients fulfills all serological efficacy criteria as required for the elderly population (aged 60 and older) at day 21 according to the respective European guidance documents. These criteria are 30% for seroconversion rate, 60% for seroprotection rate and 2 for geometric mean ratio (GMR).

Main secondary objectives:

1. The immune response of the H1N1 vaccine is at least as effective in transplanted patients as in the healthy volunteers after one administration. For orientation in the assessment a non-inferiority-margin of 0.45 for the ratio of the geometric mean titers (GMTs) of transplanted patients and age-matched healthy volunteers at day 21(visit 2) will be used and reflects what can be demonstrated with given sample size.
2. The primary and the first main secondary objective will also be evaluated for the other two virus strains (H3N2 and type B) of the trivalent vaccination.

Further secondary objectives (applying on each of the three virus strains):

1. The serological efficacy criteria as outlined for the elderly in the European guidance documents (EMEA/CPMP/BWP/214/96) are fulfilled for transplanted patients at day 42 and 280.
2. Comparison of the serological efficacy criteria seroprotection and seroconversion rates between transplanted patients and age-matched healthy volunteers.
3. The serological efficacy criteria as outlined in the European guidance documents are fulfilled for age-matched healthy volunteers at day 21 (visit 2), 42 (visit 3) and 280 (visit 4). These criteria are 40% for seroconversion rate, 70% for seroprotection rate and 2.5 for GMR.
4. Comparison of immune response in relation to immunosuppressive medication in transplant subjects at day 21, 42 and 280.
5. All serological assessments and group comparisons measured by microneutralization (MN) for transplanted patients and age-matched healthy volunteers will be performed in line with HI analyses at all time points.

Comparison of the safety of the trivalent adjuvanted vaccine overall, as well as in transplant patients and age-matched healthy volunteers separately.

Methodology:

The primary analysis for H1N1 at day 21 was performed in all transplanted patients that had evaluable blood samples at day 0 and 21. Seroconversion and seroprotection rates and respective 95% Wald confidence intervals (CI) were calculated. The geometric mean titer at day 0 and 21 as well as the geometric mean ratio (GMR, day 21 / day 0) were computed with respective 95% CIs (back-transformed 95% t-Confidence-Intervals for the natural-log-transformed data) according to the study protocol. This study is successful, if all three point estimates (seroconversion rate, seroprotection rate, GMR) pass the corresponding efficacy criteria of the elderly people (adult subjects aged over 60) at day 21. These criteria are 30% for seroconversion rate, 60% for seroprotection rate and 2 for GMR. Analyses were performed for all transplanted patients as well as for the subgroup of transplanted patients that were seronegative at baseline, i.e. patients that already have seroprotection at baseline were excluded. Furthermore subgroup analyses were performed for different types of transplantation (liver vs. kidney) and different types of immunosuppressive

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agents (Tacrolimus vs. Ciclosporin, Corticosteroids vs. no Corticosteroids).
As key secondary analyses, serological efficacy of H1N1 in healthy volunteers and serological efficacy of the two other virus strains H3N2 and typeB in healthy and in transplanted subjects were investigated. These analyses were carried out in line with the primary analysis.
Another key secondary objective was to compare the serological response towards H1N1 between transplanted and healthy subjects. Log E(GMT) values of transplanted and age-matched healthy volunteers at day 21 were compared computing a two-sample t-test for independent groups (Tx – Healthy) and the corresponding two-sided 95% confidence interval. The pre-specified non-inferiority margin was set to 0.45. This means, non-inferiority of the H1N1 immune response in transplant patients compared to healthy controls can be concluded, if the respective lower boundary of the two-sided 95% confidence interval does not exceed 0.45.
Further secondary and safety analyses were performed according to the study protocol.
All statistical analyses were conducted using SAS (Version 9.2 for analyses of day 0-42, version 9.3 for long-term results). Serological data, provided by Novartis, contained left censored titer values due to a detection limit of 10. All entries "<10" were set to a titer of 5 before analysis.

Number of patients (planned and analysed):
planned: 60 transplant recipients (Tx) and 60 age-matched healthy controls (HC)
recruited: 61 subjects for each group (visit 1)
analysed:
- visit 2 (primary endpoint, day 21): n=57 for Tx and n=59 for HC
- visit 3 (secondary endpoint, day 42): n=56 for Tx and n=60 for HC
- visit 4 (secondary endpoint, day 280): n=57 for Tx and n=55 for HC

Diagnosis and main criteria for inclusion:
Transplant Recipients:

- Adult subjects 18-60 years of age who have undergone prior renal, cardiac, liver, lung, or bone marrow transplantation for any reason, more than 3 months prior to enrolment
- Patients able to visit the outpatient clinic with a life expectancy of at least one year
- Patients who receive any immunosuppressive treatment currently taken to prevent organ rejection

Healthy Adults:

- Adult subjects 18-60 years of age
- Healthy individuals as determined by medical history, physical assessment and clinical judgment of the investigator
- Within the same age category (+/- 5 years) like the incidental transplanted patient

Transplant Recipients and Healthy Adults:

- Individuals who are able to comply with all study procedures and are available for all clinic visits scheduled in the study
- Women of child-bearing potential (WOCBP) must have used an acceptable contraceptive method for at least 2 months prior to study entry until 3 weeks after the vaccination:
    - Female of childbearing potential is defined as an onset of menarche or pre-menopausal female capable of becoming pregnant. This does not include females who meet any of the following conditions: (1) menopause at least 2 years earlier, (2) tubal ligation at least 1 year earlier, or (3) total hysterectomy
    - Acceptable birth control methods are defined as one or more of the following:
        - Hormonal contraceptive (such as oral, injection, transdermal patch, implant, cervical ring)
        - Barrier (condom with spermicide or diaphragm with spermicide) each and every time during intercourse
        - Intrauterine device (IUD)
        - Monogamous relationship with vasectomized partner. Partner must have been vasectomized for at least six months prior to the subject's study entry

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Test product, dose and mode of administration, batch number:
Product: Fluad®
Dose: 0.5ml solution containing combination of WHO recommend Influenza antigens and MF59 adjuvans
Mode of administration: intramuscular, single application
Batch / Lot Number: 105003A

Duration of treatment:
Influenza vaccination is generally recommended once a year, typically in the fall / winter. Follow-up period was 280 days.

Reference therapy, dose and mode of administration, batch number:

n/a

Criteria for evaluation:

Efficacy:

The aims of the study was to show that transplanted patients fulfil the serological efficacy criteria for elderly people (> 65 years) after 21 days when immunized with the trivalent Influenza vaccine including H1N1, H3N2 and B antigen, namely

1. Seroprotection (SP) rate > 60%
2. Seroconversion (SC) rate > 30%
3. GMR > 2

Secondary objectives included:

- Comparing the efficiency of the immune response of the H1N1 vaccine in transplanted patients and in the healthy volunteers after a single administration. A non-inferiority margin of 0.45 for the ratio of the geometric mean titers (GMTs) of transplanted patients and age-matched healthy volunteers at day 21 will be used.

Further exploratory secondary objectives (applying on each of the three virus strains):

- The serological efficacy criteria as outlined for the elderly in the European guidance documents (EMEA/CPMP/BWP/214/96) are fulfilled for transplanted patients at day 42 and 280.
- Comparison of the serological efficacy criteria „seroprotection“ and „seroconversion rates“ between transplanted patients and age-matched healthy volunteers.
- The serological efficacy criteria as outlined in the European guidance documents are fulfilled for age-matched healthy volunteers at day 21, 42 and 280. These criteria are 40% for seroconversion rate, 70% for seroprotection rate and 2.5 for GMR.
- Comparison of immune response in relation to immunosuppressive medication in transplant subjects at day 21, 42 and 280.
- All serological assessments and group comparisons measured by microneutralization (MN) for transplanted patients and age-matched healthy volunteers will be performed in line with HI analyses at all time points.

Safety:

Comparison of the safety of the trivalent adjuvanted vaccine overall, as well as in transplant patients and age-matched healthy volunteers separately.

Statistical methods:
See Methodology section

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Summary - Conclusions

Efficacy Results:

Transplant recipients:

In this study all serological criteria in transplanted patients were achieved for H1N1 (day 21: SP=84.2%, SC=59.6%, GMR=9.4) and for H3N2 (day 21: SP=96.5%, SC=70.2%, GMR=10.4). All criteria were also fulfilled in transplanted patients seronegative at baseline. Serological efficacy of H1N1 and H3N2 could be shown for day 21, day 42 and even day 280.

In short-term visits (up to day 42) not only the point estimates, but also the lower limits of the 95%-CIs fulfill the thresholds of the European guidance documents. In addition both, point estimates and the lower limits of the 95%-CIs, are also above the criteria that are stipulated for healthy adults younger than 65.

The long-term follow-up for H1N1 and H3N2 reveals that several subgroups no longer fulfill the serological efficacy criteria. Patients with kidney transplants and patients receiving corticosteroids have seroprotection rates below 60%.

Serological efficacy criteria were also achieved for type B in transplanted patients (day 21: SP=96.5%, SC=52.6%, GMR=5.1) and in transplanted patients seronegative at baseline for visits at day 21 and 42. The number of seronegative patients at baseline was smaller in type B than in H1N1 or H3N2. Serological efficacy criteria were not fulfilled after 280 days: all three point estimates are below the respective thresholds.

Healthy controls:

In this study all serological criteria were achieved for H1N1 and H3N2 in healthy volunteers as well as in healthy volunteers that were seronegative at baseline, even for the lower limits of the 95%-CIs.

At day 21 and at day 42 all serological criteria were achieved for type B in healthy volunteers as well as in healthy volunteers that were seronegative at baseline, even for the lower limits of the 95%-CIs. Similarly to the situation in transplanted patients, serological efficacy for type B is not achieved in the long-term visit at day 280.

Comparison of serological efficacy between transplanted patients and healthy controls:

As a key secondary objective, transplanted patients and age-matched healthy volunteers were compared by the ratio of their geometric mean titers (GMTs) at day 21, defined as GMR = $GMT_{21}(Tx)$ / $GMT_{21}(H)$. A non-inferiority margin of 0.45 was defined prior to the study.

For H1N1, a GMR of 0.68 was found with a two-sided 95% confidence interval of [0.35, 1.33]. The lower boundary was smaller than 0.45, thus non-inferiority can not be concluded. H1N1 immune response of transplanted patients might be relevantly inferior to that in healthy controls.

Regarding H3N2, geometric mean titers in transplanted patients are lower than in healthy volunteers (day 21: GMR=0.82), but the lower limit of the confidence interval for the ratio is above 0.45 at day 21 and 42, thus indicating non-inferiority.

Immune response to type B is higher in transplanted patients than in healthy subjects, and non-inferiority could be shown for type B.

Safety Results:

AE:

Within 6 weeks after injection, 143 non-serious adverse events were recorded, which occurred in a total of 47 study participants (25x TX, 22x Healthy). Most of these adverse events had not been considered to be in causal relationship to the study medication.

A total of 45 adverse events are probably or surely associated with the study medication. A listing of all unsolicited observed AEs with probable or assured causality reveals that only mild (toxicity grade=1) AEs occurred: arthralgia, chills, fatigue, haematoma, headache, hyperhidrosis, injection site erythema, injection site induration, injection site pain, injection site swelling, malaise, myalgia, pain, vaccination site warmth.

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SAE:

A total of 14 serious adverse events occurred in this trial, some of are listed for more than one term (Table 1).

System Organ Class	Total	Solid organ or bone marrow transplants	Healthy volunteers
Preferred Term			
Cardiac disorders	1	1	0
Atrial fibrillation	1	1	0
Gastrointestinal disorders	1	0	1
Rectal haemorrhage	1	0	1
General disorders and administration site conditions	1	1	0
Device leakage	1	1	0
Hepatobiliary disorders	5	5	0
Cholangitis	1	1	0
Hepatic function abnormal	1	1	0
Liver disorder	1	1	0
Hypertransaminasaemia	2	2	0
Immune system disorders	4	4	0
Liver transplant rejection	2	2	0
Transplant rejection	2	2	0
Infections and infestations	2	2	0
Liver abscess	1	1	0
Chest wall abscess	1	1	0
Injury, poisoning and procedural complications	1	1	0
Procedural complication	1	1	0
Investigations	1	1	0
Transaminase increased	1	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	2	0
Hepatic neoplasm malignant recurrent	1	1	0
Cervix carcinoma stage 0	1	1	0

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Within 6 weeks after injection, seven serious adverse events occurred in a total of four transplanted patients. Only one of these SAEs was assessed by the sponsors´ delegate for pharmacology as being possibly related to IMP Fluad®, yet unexpected according to the Summary of Product Characteristics (SPC): An 51 year-old male liver transplant patient was hospitalized 13 days after application of the IMP due to a chest wall abscess and liver abscess. Drainage of the abscess was implemented. Microbiological findings in the pus included E.coli, Prevotella species and Streptococcus. Antibiotic therapy was induced with metronidazol and imipenem. The patient fully recovered. This SUSAR was reported to the NCA and IEC on 08 June 2011 (DE-HCTC-000227). A follow-up was reported on 15 July 2011.

Within 9 months after injection, 14 serious adverse events occurred in a total of eight transplanted patients and one healthy subject. Only one of these SAEs was assessed to have a causal relationship to the study vaccine, see previous paragraph.

Conclusion:
Fluad® seasonal vaccine is effective and safe in transplant recipients and in healthy controls even after long-term follow-up.

Date of the report:
April 19th, 2013