SYNOPSIS

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TITLE OF STUDY

An Open-label, Multi-centre, Randomised, Comparative Study of the Immunogenicity and Safety of an Inactivated Split-Virion Influenza Vaccine Administered by Intradermal Route (Flu-ID 15µg) Versus an Inactivated Adjuvanted Influenza Vaccine Administered by Intramuscular Route (Addigrip® 15µg) in Subjects 65 Years of Age or Older.

Study Identification Number: FID01C
EudraCT Number: 2007-002861-11

COORDINATING INVESTIGATORS

- Belgium: Professor Pierre VAN DAMME, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk.
- France: Doctor Robert ARNOU, 2 Avenue de Chanzy, 49000 Angers.

STUDY CENTRES

- 10 active centres, 3 in Belgium and 7 in France.

PUBLICATION (REFERENCE)

- None at the time of report writing.

STUDIED PERIOD	2 months.	**Phase of development**
First Visit First Subject:	17 October 2007.	Phase 3
Last Visit Last Subject:	13 December 2007.	

OBJECTIVES

PRIMARY OBJECTIVE (IMUNOGENICITY)

- To demonstrate that the influenza vaccine administered by intradermal (ID) route at the dose of 15 microgram (µg) is at least as immunogenic as the adjuvanted influenza vaccine administered by intramuscular (IM) route at the same dosage in terms of antibody titres (haemagglutination inhibition [HI] method) for the three strains on Day 21 post-vaccination.

Hypothesis:

- The immunogenicity observed in the ID group is non-inferior to that of the adjuvanted IM group for each strain (A/H3N2, A/H1N1, and B) in terms of antibody titres

And if the above hypothesis is demonstrated for all three strains:

- The immunogenicity observed in the ID group is superior to that of the adjuvanted IM group in terms of antibody titres for at least two strains.

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OBJECTIVES (CONTINUED)

SECONDARY OBJECTIVES

Immunogenicity:

- To demonstrate that the influenza vaccine administered by ID route at a dose of 15 µg is at least as immunogenic as the adjuvanted influenza vaccine administered by IM route at the same dosage in terms of antibody titres (single-radial haemolysis [SRH] method) for the three strains on Day 21 post-vaccination using the same hypothesis as described above
- To describe the immune response (HI and SRH methods) 21 days after vaccination between the ID group versus the adjuvanted IM group for each strain in terms of:
  - Geometric mean of individual post/pre-antibody titres ratio (GMTR)
  - Post-vaccination seroprotection rate
  - Seroconversion or significant increase rate
- To describe the compliance of both vaccines (HI and SRH methods) regarding the *Immunogenicity Criteria Specific for Elderly Subjects* defined by the European Medicines Agency (EMEA) in the *Note for Guidance* on Harmonisation of Requirements for Influenza vaccines (CPMP/BWP/214/96).

Safety:

- To describe the safety profile after vaccination in each group.

Acceptability:

- To describe the pain at the injection site using a Verbal Rating Scale (VRS)
- To describe the comfort of the injection using a self-administrated Vaccination Comfort Questionnaire (VCQ).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Subjects aged 65 years or older on the day of inclusion. Informed consent form (ICF) signed before any study procedure. No systemic hypersensitivity or life-threatening adverse reaction (AR) to egg proteins, chick proteins, or any of the vaccine components. No congenital or acquired immunodeficiency, or immunosuppressive therapy in the past 6 months or long-term systemic corticosteroid therapy. No administration of blood or blood-derived products (including immunoglobulins) in the past 3 months. No vaccination in the past 4 weeks (in the past 6 months for influenza vaccines) and/or influenza vaccine by ID route.

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TEST VACCINE, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

- **Flu-ID 15µg:** Influenza vaccine (split virion, inactivated) (2007/2008 Northern Hemisphere formulation)
  - Presentation: Suspension for injection contained in a pre-filled full-glass syringe equipped with a Becton Dickinson micro-delivery system (ID system)
  - Dose: 0.1 mL
  - Route: ID (deltoid area)
  - On site storage: +2°Celsius (°C) to +8°C
  - Batch number: S4198F01 (expiry date: 31 January 2008).

REFERENCE VACCINE, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

- **Addigrip®:** Influenza virus surface antigens (inactivated, adjuvanted with MF59C.1) (2007/2008 Northern Hemisphere formulation)
  - Presentation: suspension for injection contained in a pre-filled full-glass syringe
  - Dose: 0.5 mL
  - Route: IM (deltoid muscle)
  - On site storage: +2°C to +8°C
  - Batch number: 79004 (expiry date: 31 May 2008).

METHODOLOGY

Open-label, multi-centre, randomised, comparative 2-parallel group study.

DURATION OF FOLLOW-UP

Immunogenicity was evaluated 21 +/- 3 days after vaccination and safety was followed up to this time. Non-serious adverse events (AEs), which were considered possibly, probably or definitely related to the study vaccine by the investigator and all serious adverse events (SAEs) that persisted at the time of Visit 2 (after Day 21) were followed up by the investigator until their complete resolution or stabilisation.

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CRITERIA FOR EVALUATION

IMMUNOGENICITY

Primary Criterion:

- Anti-haemagglutinin (anti-HA) antibody titres (1/dilution [1/dil] - HI method) for the three strains on Day 21.

Secondary Criteria:

- Anti-HA antibody titres (square millimetre [mm²] - SRH method) for the three strains on Day 21
- Anti-HA individual titre ratios (GMTR Day 21/Day 0] (HI and SRH methods)
- Post-vaccination seroprotection status (anti-HA individual titre >=40 [1/dil] or >=25 mm² on Day 21 for HI or SRH method, respectively)
- Seroconversion or significant increase status on Day 21 (HI and SRH methods):
  - *Seroconversion:* anti-HA individual post-vaccination titre >=40 (1/dil – HI method) or >=25 mm² (SRH method) for subjects with a pre-vaccination anti-HA individual titre <10 (1/dil – HI method) or <=4 mm² (SRH method)
  - *Significant increase:* >=4-fold increase (HI method) or >=1.5-fold increase (SRH method) from pre- to post-vaccination anti-HA individual titre for subjects with a pre-vaccination anti-HA individual titre >=10 (1/dil – HI method) or >4 mm² (SRH method).

SAFETY

- From Day 0 to Day 7, occurrence, time to onset, number of days of occurrence and intensity of solicited [prelisted in the subject's diary card (DC) and case report form (CRF)] ARs by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) or lowest level term (LLT):
  - *Injection-site adverse reactions* (ISRs): pain, erythema, swelling, induration, ecchymosis (PT haemorrhage), and pruritus
  - *Systemic ARs*: pyrexia (rectal equivalent temperature >=38.0°C), headache, malaise, myalgia and shivering (PT chills)
- From Day 0 to Day 3, occurrence of some solicited ARs occurring after vaccination as defined by the EMEA *Note for Guidance* [CPMP/BWP/214/96]: injection site induration >5 cm observed for >3 consecutive days, injection site ecchymosis, pyrexia (rectal equivalent temperature >38.0°C) for >=24 hours, malaise, and shivering
- From Day 0 to Visit 2, occurrence, nature (MedDRA PT), time to onset, duration, intensity, and relationship to vaccination (only for systemic AEs) of unsolicited ISRs and systemic AEs
- From Day 0 to Visit 2, occurrence, nature (MedDRA PT), time to onset, duration, intensity and relationship to vaccination (only for systemic AEs) of SAEs.

ACCEPTABILITY

- Day 0: intensity of pain by VRS ranging from 0 (no pain) to 5 (unbearable pain)
- Day 21: answers to the 21 items-VCQ using 5-point Likert type scale ranging from 1 (none or not at all) to 5 (all the time or extremely).

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STATISTICAL METHODS

IMMUNOGENICITY

Primary Objective:

The primary statistical analysis was performed on the Per Protocol Set (main analysis for the non-inferiority demonstration) and on the Full Analysis Set (main analysis for the superiority demonstration).

For each strain, the primary endpoint was the ratio of the post-vaccination geometric mean titres (GMTs) measured by the HI method between vaccine groups.

- **Non-inferiority hypotheses** were as follows for each strain:

  H0: GMT(aIM) / GMT(ID) >=1.5 H1: GMT(aIM) / GMT(ID) <1.5

  The ID group (ID - test) was considered as non-inferior to the adjuvanted IM group (aIM - reference) if the hypothesis H0 was rejected for all three strains.

If non-inferiority was demonstrated for the ID group (test) for each strain, superiority was then tested.

- **Superiority hypotheses** were as follows for each strain:

  H0: GMT(aIM) / GMT(ID) >=1 H1: GMT(aIM) / GMT(ID) <1

  The ID group (ID - test) was considered superior to the adjuvanted IM group (aIM - reference) if the hypothesis H0 was rejected for at least two strains.

For both non-inferiority and superiority, the statistical methodology was based on the use of a two-sided 95% confidence interval (CI) around the GMT(aIM) to GMT(ID) ratio.

- **Sensitivity analysis:** For each strain, an analysis of covariance (ANCOVA) model with the age of the subject at vaccination as covariate, the vaccine group and centre as fixed effects and the natural log transformed post-vaccination individual titre as response was set up.

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STATISTICAL METHODS (CONTINUED)

Secondary Objectives:

The secondary statistical analyses were performed on the Per Protocol Set (PPS), the Full Analysis Set (FAS) and/or Other Immunogenicity Analysis Sets.

- With the SRH method:
  - Comparison of the post-vaccination GMTs between vaccine groups using the same statistical method as describe above
  - Comparison of the post-vaccination GMTs between vaccine groups adjusted on the pre-vaccination titres (ANCOVA) using the same statistical method as describe above (except sensitivity analysis).
- With both the SRH and HI methods
  - Analysis by groups and in the subgroups according to age (<75 years and >=75 years):
    - Post-vaccination seroprotection rates and two-sided 95% CI values
    - GMTR and two-sided 95% CI values
    - Seroconversion or significant increase rates and two-sided 95% CI values
  - Compliance of both vaccines regarding *the Immunogenicity Criteria Specific for Elderly Subjects* as defined by the EMEA *Note for Guidance* [CPMP/BWP/214/96]:
    - Proportion of subjects achieving post-vaccination seroprotection >60%
    - GMTR >2
    - Proportion of subjects with seroconversion or significant increase in titres >30%
  - Differences between groups and in the subgroups of subjects not seroprotected on Day 0 for post-vaccination seroprotection rates, GMTR and seroconversion or significant increase rate and two-sided 95% CI values.

SAFETY

Safety statistical analyses were performed on the Safety Set. The numbers and percentages of subjects experiencing all, solicited and unsolicited, ISRs, systemic AEs and systemic ARs are described (with their corresponding 95% CI for global summary of safety and solicited ARs) by group and according to time to onset, intensity, duration. SAEs and discontinuations due to AEs were described in detail.

ACCEPTABILITY

- VRS: descriptive analysis
- VCQ: before studying the vaccine effect, assessment of the quality of completion of the VCQ and reassessment of the psychometric qualities of the tool were performed. Qualitative and quantitative variables were described. Non parametric tests were used to compare groups, ANCOVA was used to compare vaccine groups, Cronbach's alpha coefficient was used when analysing VCQ internal consistency reliability, and Spearman correlation coefficient was used when analysing the relationship between quantitative variables. Statistical significance threshold was set at 5% ($p<0.05$). Specific Sets of subjects were used for these analyses.

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NUMBER OF SUBJECTS (PLANNED AND ANALYSED)

- Planned: 790 subjects (395 subjects per group)
- Selected: 796 subjects (with ICF signed)
- Randomised: 795 subjects (see Table 1)

Table 1: Disposition of Subjects (Randomised Set)

	Flu-ID 15µg	**Addigrip®**
	n subjects (%)	
Randomised	398 (100)	397 (100)
Vaccinated	398 (100)	397 (100)
Completed	397 (99.7)	396 (99.7)
Withdrawn	1 (0.3)	1 (0.3)
Serious adverse event	1 (0.3) (a)	0
Voluntary withdrawal not due to an adverse event	0	1 (0.3) (b)

Percentages are based on the number of randomised subjects.
(a) Cardiac arrest leading to death on Day 20 assessed as not related to study vaccine
(b) Voluntary withdrawal on Day 20

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NUMBER OF SUBJECTS (PLANNED AND ANALYSED) (CONTINUED)

- Analysed: see Table 2.

Table 2: Analysis Sets of Subjects

	Flu-ID 15µg	**Addigrip®**
	n subjects (%)	
Randomised Set	398 (100)	397 (100)
Full Analysis Set	395 (99.2)	395 (99.5)
Per Protocol Set – HI method	390 (98.0)	385 (97.0)
Per Protocol Set– SRH method (a)	389 (97.7)	382 (96.2)
Other Immunogenicity Analysis Set – HI method		
A/Solomon (H1N1)	395 (99.2)	395 (99.5)
A/Wisconsin (H3N2)	395 (99.2)	395 (99.5)
B/Malaysia	395 (99.2)	395 (99.5)
Other Immunogenicity Analysis Set – SRH method (b)		
A/Solomon (H1N1)	391 (98.2)	389 (98.0)
A/Wisconsin (H3N2)	391 (98.2)	388 (97.7)
B/Malaysia	391 (98.2)	389 (98.0)
Safety Set	398 (100)	397 (100)

Percentages are based on the number of randomised subjects. Subjects were analysed according to the vaccine they actually received except for the randomised set.

(a) The reason for excluding 4 additional subjects from the Per Protocol Set (1 in the Flu-ID 15µg group and 3 in the Addigrip® group) was post-vaccination BS not tested with the SRH method

(b) The reasons for excluding 11 additional subjects from the Other Immunogenicity Analysis Sets (4 in the Flu-ID 15µg group and 6 or 7 according to the vaccine strain in the Addigrip® group) were pre- and/or post-vaccination BS not tested with the SRH method

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SUMMARY - CONCLUSIONS

DEMOGRAPHY

Participants were 46.5% male (N=370) and 53.5% female (N=425) whose ages ranged from 60.3 to 94.2 years (mean age +/- standard deviation [SD] was 74.28 +/- 6.43 years). 89.9% of the subjects in both groups had at least one past and/or current significant medical history and 52.7% had a risk factor (mainly of heart disease). 8.4% of the subjects reported allergy history. For the 2006/2007 influenza season, 72.5% of the subjects have been vaccinated against influenza virus. The groups were comparable at inclusion.

IMMUNOGENICITY RESULTS

Primary Objective:

- Comparison of Post-Vaccination GMT With the HI Method

On the PPS, non-inferiority of Flu-ID 15µg compared to Addigrip® was demonstrated for the A/Solomon and the B strains as the upper bounds of the 95% CI of the ratio of post-vaccination GMT Addigrip®/Flu-ID 15µg were below 1.5.

The primary immunogenicity hypothesis of the non-inferiority of Flu-ID 15µg compared to Addigrip® was not met since the upper bound of the 95% CI was slightly above 1.5 (1.53) for the A/Wisconsin strain (Table 3).

Table 3: Geometric Mean Titres (GMTs) of the Three Vaccine Strains on Day 21, Ratio of Post-Vaccination GMTs and Non-Inferiority Analysis – HI Method (Per Protocol Set)

1/dil	**Flu-ID 15µg (N=390)**	**Addigrip® (N= 385)**	**GMT Ratio Addigrip®/Flu-ID 15µg [95% CI]**	**Non-inferiority (a)**
	Post-vaccination GMT [95% CI]			
A/Solomon (H1N1)	108.3 [95.4;123.0]	122.1 [109.1;136.7]	1.13 [0.95;1.34]	Yes
A/Wisconsin (H3N2)	259.9 [233.5;289.3]	341.4 [306.7;380.1]	1.31 [1.13;1.53]	No
B/Malaysia	36.9 [33.6;40.5]	39.9 [36.4;43.8]	1.08 [0.95;1.23]	Yes

(a) Non-inferiority of each strain was demonstrated (yes) if the upper bound of the 95% CI was <1.5

The sensitivity analysis provided similar results.

The analysis of superiority of Flu-ID 15µg compared to Addigrip® was not performed as non-inferiority was not demonstrated for all three strains.

A comparison of the post-vaccination GMT between vaccine groups adjusted on the pre-vaccination titres (ANCOVA) was performed as a *post-hoc* analysis. Non-inferiority of Flu-ID 15µg compared to Addigrip® was demonstrated for the three strains (the upper bound of the 95% CI for A/Wisconsin was 1.42 on the PPS).

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IMMUNOGENICITY RESULTS (CONTINUED)

Secondary Objectives:

- Comparison of Post-Vaccination GMT With the SRH Method

On the PPS, non-inferiority of Flu-ID 15µg compared to Addigrip® was demonstrated for the three strains as the upper bounds of the 95% CI of the ratio of post-vaccination GMT Addigrip®/Flu-ID 15µg were all below 1.5.

The immunogenicity hypothesis of the non-inferiority of Flu-ID 15µg compared to Addigrip® was met with the SRH method (Table 4).

Table 4: Geometric Mean Titres (GMTs) of the Three Vaccine Strains on Day 21, Ratio of Post-Vaccination GMTs and Non-Inferiority Analysis – SRH Method (Per Protocol Set)

mm²	**Flu-ID 15µg (N=389)**	**Addigrip® (N= 382)**	**GMT Ratio Addigrip®/Flu-ID 15µg [95% CI]**	**Non-inferiority (a)**
	Post-vaccination GMT [95% CI]			
A/Solomon (H1N1)	46.4 [41.6;51.8]	53.9 [49.0;59.3]	1.16 [1.00;1.34]	Yes
A/Wisconsin (H3N2)	39.3 [35.6;43.3]	46.2 [42.1;50.7]	1.18 [1.03;1.34]	Yes
B/Malaysia	66.5 [60.8;72.8]	68.9 [62.9;75.3]	1.03 [0.91;1.17]	Yes

(a) Non-inferiority of each strain was demonstrated (yes) if the upper bound of the 95% CI was <1.5

The sensitivity analysis provided similar results.

The analysis of superiority was performed on the FAS, and superiority was not demonstrated for any of the three strains.

The comparison of the post-vaccination GMT between vaccine groups adjusted on the pre-vaccination titres (ANCOVA) provided similar results.

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IMMUNOGENICITY RESULTS - Secondary Objectives (CONTINUED)

- GMTs, GMTRs, Seroprotection, Seroconversion or Significant Increase Rate, EMEA Criteria and Differences Between Groups With both the HI and SRH Methods

HI Method

In both groups, the three EMEA criteria were met for the two A strains and one of the three criteria (GMTR) was met for the B strain. Overall, both vaccine groups met at least one EMEA criterion for each strain (Table 5).

Table 5: Post/Pre GMT Ratio (GMTR), Post-Vaccination (Day 21) Seroprotection and Seroconversion or Significant Increase Rates, and Criteria as Listed in the EMEA *Note for Guidance* for the Three Vaccine Strains – HI Method (Other Immunogenicity Analysis Set)

1/dil	Flu-ID 15µg (N=395)			Addigrip® (N=395)		
	A/ Solomon (H1N1)	A/ Wisconsin (H3N2)	B/ Malaysia	A/ Solomon (H1N1)	A/ Wisconsin (H3N2)	B/ Malaysia
GMTR (a) [95% CI]	8.2 [7.2;9.2]	4.4 [3.8;5.0]	2.5 [2.3;2.7]	9.0 [8.0;10.0]	4.9 [4.3;5.6]	2.4 [2.2;2.6]
EMEA criteria (d)	Yes	Yes	Yes	Yes	Yes	Yes
	n (%): number and percentage of subjects					
Day 21 Sero-protection rate (b) [95% CI]	321 (81.3) [77.1;85.0]	383 (97.0) [94.8;98.4]	202 (51.1) [46.1;56.2]	344 (87.1) [83.4;90.2]	384 (97.2) [95.1;98.6]	220 (55.7) [50.6;60.7]
EMEA criteria (d)	Yes	Yes	No	Yes	Yes	No
Seroconversion or significant increase rate (c) [95% CI]	272 (68.9) [64.0;73.4]	188 (47.6) [42.6;52.6]	94 (23.8) [19.7;28.3]	288 (72.9) [68.2;77.2]	199 (50.4) [45.3;55.4]	90 (22.8) [18.7;27.2]
EMEA criteria (d)	Yes	Yes	No	Yes	Yes	No

(a) Post/pre-vaccination (Day 21/Day 0) GMT ratio
(b) Seroprotection is defined as a antibody titre >=40 (1/dil)
(c) Seroconversion is defined as an antibody titre >=40 (1/dil) on Day 21 when antibody titre was <10 (1/dil) on Day 0. Significant increase is defined as a >=4-fold increase in antibody titre from Day 0 to Day 21 when antibody titre was >=10 (1/dil) on Day 0
(d) Immunogenicity criteria specific for elderly subjects as defined by the EMEA *Note for Guidance* [CPMP/BWP/214/96]: GMTR >2, proportion of subjects achieving post-vaccination seroprotection >60%, and proportion of subjects with seroconversion or significant increase in titres >30%

It was observed that for the three strains, the two groups were not statistically different for GMTRs and for seroconversion or significant increase rates. For seroprotection rates, it was also observed that the two groups were not statistically different for the A/Wisconsin and B strains while a statistically significant difference was observed for the A/Solomon strain although not pre-defined hypothesis and despite high seroprotection rates in both groups (81.3% in the Flu-ID 15µg group and 87.1% in the Addigrip® group on the FAS).

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IMMUNOGENICITY RESULTS - Secondary Objectives (CONTINUED)

SRH Method

The three EMEA criteria were met for the three strains in both vaccine groups (Table 6).

Table 6: Post/Pre GMT Ratio (GMTR), Post-Vaccination (Day 21) Seroprotection and Seroconversion or Significant Increase Rates, and Criteria as Listed in the EMEA *Note for Guidance* for the Three Vaccine Strains – SRH Method (Other Immunogenicity Analysis Set)

mm^2	**Flu-ID 15µg**			**Addigrip®**		
	N=391	**N=391**	**N=391**	**N= 389**	**N= 388**	**N= 389**
	A/ Solomon (H1N1)	**A/ Wisconsin (H3N2)**	**B/ Malaysia**	**A/ Solomon (H1N1)**	**A/ Wisconsin (H3N2)**	**B/ Malaysia**
GMTR (a) [95% CI]	6.2 [5.5;7.0]	3.6 [3.2;4.1]	2.3 [2.0;2.5]	6.9 [6.1;7.8]	3.7 [3.3;4.2]	2.5 [2.2;2.8]
EMEA criteria (d)	Yes	Yes	Yes	Yes	Yes	Yes
	n (%): number and percentage of subjects					
Day 21 Sero-protection rate (b) [95% CI]	331 (84.7) [80.7;88.1]	323 (82.6) [78.5;86.2]	357 (91.3) [88.1;93.9]	351 (90.2) [86.8;93.0]	339 (87.4) [83.6;90.5]	359 (92.3) [89.2;94.7]
EMEA criteria (d)	Yes	Yes	Yes	Yes	Yes	Yes
Seroconversion or significant increase rate (c) [95% CI]	299 (76.5) [71.9;80.6]	219 (56.0) [50.9;61.0]	145 (37.1) [32.3;42.1]	314 (80.7) [76.4;84.5]	233 (60.1) [55.0;65.0]	147 (37.8) [33.0;42.8]
EMEA criteria (d)	Yes	Yes	Yes	Yes	Yes	Yes

(a) Post/pre-vaccination (Day 21/Day 0) GMT ratio;
(b) Seroprotection is defined as a antibody titre >=25 mm^2;
(c) Seroconversion is defined as an antibody titre >=25 mm² on Day 21 when antibody titre was <=4 mm² on Day 0. Significant increase is defined as a >=1.5-fold increase in antibody titre from Day 0 to Day 21 when antibody titre was >4 mm² on Day 0;
(d) Immunogenicity criteria specific for elderly subjects as defined by the EMEA *Note for Guidance* [CPMP/BWP/214/96]: GMTR >2, proportion of subjects achieving post-vaccination seroprotection >60%, and proportion of subjects with seroconversion or significant increase in titres >30%

No statistically significant differences were observed between the two groups for the three parameters and for the three strains, except for the seroprotection rate to the A/Solomon strain although not pre-defined hypothesis and despite high seroprotection rates in both groups (84.3% in the Flu-ID 15µg group and 90.1% in the Addigrip® group on the FAS). The results obtained with the SRH method were similar to those obtained with the HI method.

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SAFETY RESULTS

More subjects reported AEs from Day 0 to Day 21 in the Flu-ID 15µg (76.9%) than in the Addigrip® group (50.4%). However both groups were comparable in terms of rate of subjects reporting systemic AEs (31.9% and 32.5% in the Flu-ID 15µg and Addigrip® groups, respectively). The difference between groups was driven by more subjects reporting ISRs in the Flu-ID 15µg (70.1%) than in the Addigrip® group (33.8%) (Table 7). No unsolicited systemic AE occurred within the 30 minutes after vaccination.

Table 7: Global Summary of Safety From Day 0 to Visit 2 (Safety Set)

		Flu-ID 15µg (N=398)	**Addigrip® (N=397)**
		n subjects (%)	
Adverse event (injection-site and systemic)	All (Day 0-Day 21)	306 (76.9)	200 (50.4)
Injection-site adverse reaction (ISR)	All (Day 0-Day 21)	279 (70.1)	134 (33.8)
	All severe	57 (14.3)	18 (4.5)
	Solicited (Day 0-Day 7)	279 (70.1)	134 (33.8)
	Solicited severe	57 (14.3)	18 (4.5)
	Unsolicited (Day 0-Day 21)	1 (0.3)	0
Systemic adverse event (AE)	All (Day 0-Day 21)	127 (31.9)	129 (32.5)
	All severe	13 (3.3)	10 (2.5)
	Unsolicited (Day 0-Day 21)	54 (13.6)	56 (14.1)
	Unsolicited severe	8 (2.0)	5 (1.3)
Systemic adverse reaction (AR)	All (Day 0-Day 21)	105 (26.4)	103 (25.9)
	All severe	8 (2.0)	7 (1.8)
	Solicited (Day 0-Day 7)	99 (24.9)	96 (24.2)
	Solicited severe	7 (1.8)	6 (1.5)
	Unsolicited (Day 0-Day 21)	14 (3.5)	11 (2.8)
	Unsolicited severe	2 (0.5)	1 (0.3)
Serious adverse event (SAE)	All (Day0-Visit2)	5 (1.3)	1 (0.3)
Serious adverse reaction	All (Day0-Visit2)	1 (0.3)	1 (0.3)
Adverse event (AE) leading to withdrawal	All (Day0-Visit2)	1 (0.3)	0

n subjects (%): number and percentage of vaccinated subjects presenting at least once the considered event.

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SAFETY RESULTS (CONTINUED)

A total of 6 subjects reported SAEs. Two of them, one in each group, were assessed by the investigator as related to the study vaccine: one case of pneumonia in the Flu-ID 15µg group which occurred on Day 1 and lasted 9 days; and one case of herpes zoster in the Addigrip® group which occurred on Day 3 and was considered as stabilised 12 days later. Two SAEs, both in the Flu-ID 15µg group, led to death: a cardiac arrest on Day 20 which led to withdrawal from the study, and a subdural haematoma which started on Day 10 and led to death after the subject's participation to the study (17 days after Visit 2). Both events were assessed by the investigator as unrelated to the vaccine injection.

All the ISRs occurred between Day 0 and Day 7, most of them before Day 4, and all except one (injection site discolouration in the Flu-ID 15µg group) were solicited. More subjects reported solicited ISRs of erythema, swelling, induration and pruritus in the Flu-ID 15µg group (63.1%, 34.2%, 32.9% and 28.1%, respectively) compared to the Addigrip® group (13.4%, 8.6%, 10.6% and 6.5%, respectively) although both groups were comparable in terms of rate of subjects reporting pain and ecchymosis (19.8% and 4.8% in the Flu-ID 15µg group, and 20.9% and 3.0% in the Addigrip® group, respectively). Most of the ISRs were of mild intensity or were <2.5 cm in both groups. More subjects reported ISRs of severe intensity in the Flu-ID 15µg group, with 14.3% (95% CI: [11.0; 18.2]) of the subjects compared to 4.5% (95% CI: [2.7; 7.1]) in the Addigrip® group. This was mainly due to erythema >=5 cm (13.3% of subjects in the Flu-ID 15µg group and 2.8% in the Addigrip® group). Most of the ISRs resolved spontaneously in 3 days or less except erythema in the Flu-ID 15µg group which lasted mainly up to 7 days.

Most of the systemic AEs and ARs occurred between Day 0 and Day 7, even before Day 4 for solicited systemic ARs in both groups. Most of the systemic ARs were solicited and both groups were comparable in terms of rate of subjects reporting each of them, pyrexia, headache, malaise, myalgia, and shivering. Most of the solicited systemic ARs were of mild intensity or <=38.5°C and unsolicited systemic AEs and ARs were mainly of mild or moderate intensity. The rates of subjects reporting solicited systemic ARs of severe intensity from Day 0 to Day 7 were low and comparable in the Flu-ID 15µg and Addigrip® groups (1.8% and 1.5%, respectively) as well as from Day 0 to Day 21 for unsolicited systemic AEs of severe intensity (2.0% and 1.3%, respectively) and unsolicited systemic ARs of severe intensity (0.5% and 0.3%, respectively). No body temperature >=39.6°C was reported. Most of the systemic AEs and ARs lasted 3 days or less.

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SAFETY RESULTS (CONTINUED)

The two groups were comparable with regards to the rates of the solicited ARs occurring from Day 0 to Day 3 after vaccination as defined by the EMEA *Note for Guidance* [CPMP/BWP/214/96] (Table 8).

Table 8: Solicited Adverse Reactions From Day 0 to Day 3 After Vaccination as Listed in the EMEA *Note for Guidance* (Safety Set)

	Flu-ID 15µg (N=398)	**Addigrip® (N=397)**
	n subjects (%)	
One adverse reaction as listed in the EMEA *Note for Guidance*	**51 (12.8)**	**55 (13.9)**
Injection site induration >5 cm for >3 consecutive days	0	0
Injection site ecchymosis	13 (3.3)	12 (3.0)
Pyrexia (rectal equivalent temperature >38.0°C) for >=24 hours	6 (1.5)	12 (3.0)
Malaise	19 (4.8)	20 (5.0)
Shivering	24 (6.0)	23 (5.8)

n subjects (%): number and percentage of vaccinated subjects presenting at least once the considered reaction

ACCEPTABILITY RESULTS

Verbal Rating Scale (VRS)

Pain at the time of injection was reported in the VRS as 'no pain' by 70.1% of subjects in the Flu-ID 15µg group compared to 77.6% of subjects in the Addigrip® group. In both groups, the responses in case of pain were distributed between 'hardly no pain', 'mild pain' or 'moderate pain'. Neither 'severe pain' nor 'unbearable pain' was reported in both groups.

Vaccination Comfort Questionnaire (VCQ)

Among the 789 subjects who returned the VCQ, 782 subjects (390 in the Flu-ID 15µg group and 392 in the Addigrip® group) completed at least one item and had not received a previous vaccination by ID route and thus were included in the Vaccine Effect Population.

The percentages of subjects answering 'not at all' or 'totally acceptable' or 'very satisfied' or 'yes, definitely' to the 21 items of the VCQ were high in both groups ranging from 62% to 93% in the Flu-ID 15µg group and from 80% to 94% in the Addigrip® group. Interestingly, 82% of subjects in the Flu-ID 15µg group and 83% of subjects in the Addigrip® group answered 'yes, definitely' to the question 'would you want to be vaccinated again next year?'.

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ACCEPTABILITY RESULTS (CONTINUED)

In both groups, mean scores of dimensions and individual items were low (i.e., up to 1.5 on a 5-point scale), and differences in scores between groups were small (less than 0.19 point for the Bother dimension).

For the Bother dimension, a statistically significant difference was found ($p<0.0001$) for the country-adjusted mean scores indicating that subjects in the Flu-ID 15µg group were more bothered by the ISRs than subjects in the Addigrip® group. Also, a statistically significant difference was found ($p=0.0479$) for the country-adjusted mean scores for the Acceptability dimension meaning that the ISRs were more acceptable for subjects in the Addigrip® group than for subjects in the Flu-ID 15µg group.

A *post-hoc* analysis performed on the subset of subjects having reported at least one ISR confirmed the difference in the Bother dimension score between groups.

CONCLUSIONS

- With the HI method, non-inferiority in antibody titres for Flu-ID 15µg compared to Addigrip® was demonstrated for the A/Solomon and B strains. For the A/Wisconsin strain non-inferiority could not be demonstrated for antibody titres and the absence of non-inferiority for this strain seems to be driven by differences in pre-vaccination titres
- With the SRH method, non-inferiority in antibody titres for Flu-ID 15µg compared to Addigrip® was demonstrated for the three strains
- With the HI method the three EMEA criteria were fulfilled for both A/Solomon and A/Wisconsin strains and one EMEA criteria (GMTR) was fulfilled for the B strain in both vaccine groups. With the SRH method the three EMEA criteria were fulfilled for the three strains in both vaccine groups
- With both HI and SRH methods, the two vaccine groups were not statistically different for GMTR, seroprotection rates and seroconversion or significant increase rates for each of the three strains except for seroprotection rate to the A/Solomon strain although not pre-defined hypothesis and despite high seroprotection rates in both groups
- The safety profile of Flu-ID 15µg was consistent with what was previously observed and both vaccines were generally well-tolerated
- While the results of subject self-administrated questionnaires reflected the increased ISRs observed in the clinical database for Flu-ID 15µg, high willingness to be vaccinated next year was reported in both groups.

DATE OF THE REPORT: 29 April 2009