GID16: The ID 15µg and 21µg groups were tested at a 2.5% alpha level (one-sided hypothesis for noninferiority). A maximum acceptable ratio of 1.5 in terms of post-vaccination GMT and a global power of 91% were chosen to calculate the sample size. Assuming for each A strain a maximal standard deviation of 0.6, and 0.5 for the B strain (from GID09 (18) trial results), 322 subjects per group were necessary to test the null hypothesis. Under the assumption that about 10% of subjects would not be evaluable, 360 subjects were needed to be included in each group. Therefore a total of 1,080 subjects were planned to be enrolled in the trial

GID17: A total of 2 580 subjects in the ID investigational vaccine group and 1 075 subjects in the IM control vaccine group gave the necessary powers for the different tests of superiority of the ID investigational vaccine group versus the IM control vaccine group in terms of seroprotection and non-superiority of the ID investigational vaccine group versus the IM reference vaccine group in terms of safety.

Randomisation
In all the 4 studies (GID15, GID23, GID16 and GID17) subjects were randomised at the time of the first vaccination. Vaccine groups were allocated using permuted block method with stratification on investigational center. For the subsequent vaccinations in GID15, a similar process has been followed to randomize the subjects to ID or IM group. For the subsequent vaccinations in GID17, only subjects having received the IM control vaccine at the previous vaccination were randomized into one of the two vaccine groups in a balanced manner; subjects having received the ID investigational vaccine at the previous vaccination were not randomized and received the ID investigational vaccine.
Blinding (masking)

All studies were double-blind for dose level and different lots of ID vaccine, but open for administration route. Study GID15 which was open, including only one dose level (9µg) of the ID vaccine.

Statistical methods

In all studies superiority was evaluated only once non-inferiority had been demonstrated.

For the studies (GID02 [Vac1], GID15, and GID23), post-vaccination GMTs were used for the demonstration of non-inferiority. The non-inferiority margin was defined as the maximum GMT ratio (GMTR) between groups. A two-fold difference in GMT can justifiably be considered as clinically important. The Applicant chose to use a more conservative ratio of 1.5 to determine non-inferiority. Statistical analysis considered the confidence interval (CI) of the differences between the $\log_{10}$ GMTs, rather than the GMT ratio, to normalize antibody distribution. If the lower limit of the 95% CI of the difference was above -0.176 (-1/1.5) for each of the three strains, non-inferiority was concluded.

Superiority was concluded if the lower limit of the 95% CI of the difference between the $\log_{10}$ GMTs of each group receiving the ID Influenza Vaccine 9µg and the IM control vaccine was above 0 (i.e. lower limit of the 95% CI of the ratio of the GMTs between groups was above 1) for all vaccine strains (Phase II studies GID02 and GID15) or at least two of the strains in GID23.

Post-vaccination GMTs were used as the primary endpoint for non-inferiority of the ID Influenza Vaccine 15µg with respect to the IM Influenza Vaccine for the studies GID16 and GID17. A ratio of 1.5 was used. Statistical analysis considered the CI of the differences between the $\log_{10}$ GMTs, rather than the GMT ratio, to normalize antibody distribution. If the lower limit of the 95% CI of the difference was above -0.176 (-1/1.5) for each of the three strains, non-inferiority was concluded.

In study GID16, superiority was assessed based on comparison of GMTs between groups; if the lower limit of the 95% CI of the difference between the $\log_{10}$ GMTs of each group receiving the ID Influenza Vaccine 15µg and the IM control vaccine was above 0 for all vaccine strains, superiority was concluded.

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In study GID17, the Applicant chose to demonstrate superiority through comparison of the post-vaccination seroprotection rates. Superiority was concluded if the two-sided 95% CI of the difference in seroprotection rates was above 0 for at least two of the vaccine strains.

A supplementary analysis to evaluate superiority in GID16 using seroprotection rates was performed by the Applicant.

RESULTS

Participant flow / Numbers analysed / Conduct of the study

GID 15
A total of 978 subjects aged from 18 to 57 years were included in the study between 19 September 2005 and 28 October 2005, and randomized to one of the two study groups:

- 588 subjects were randomized in the ID 9µg group
- 390 subjects were randomized in the IM 15µg group

Enrolment stopped prior to full enrolment (1,000 subjects), because the inclusion period was shortened. However, the lower number of subjects included did not impact the primary objective of the study.

GID23
A total of 2 255 subjects aged from 18 to 60 years were included in the study between 11 September 2006 and 31 October 2006, and randomized to one of the four study groups.
The disposition of subjects in the four groups was as follows:

- 604 subjects were randomized in the ID 9µg Lot 1 group
- 596 subjects were randomized in the ID 9µg Lot 2 group
- 603 subjects were randomized in the ID 9µg Lot 3 group
- 452 subjects were randomized in the IM 15µg group

GID16
A total of 1 107 subjects aged >60 years were included in the study and randomized to one of the three study groups:

- 370 were randomized to the ID 15µg group
- 369 were randomized to the ID 21µg group
- 368 were randomized to the IM 15µg group

All subjects received the annual formulation of Influenza Vaccine by the IM route 3 months after the first vaccination to offer the subjects protection against the WHO influenza strains recommended for the 2006 Southern Hemisphere.

GID17
A total of 3 707 subjects aged >60 years were included in the study between 11 September 2006 and 31 October 2006, and randomized to one of the two study groups:

- 2 618 were randomized to the ID 15µg group
- 1 089 were randomized to the IM 15µg group

Subjects were re-randomized for the second vaccination so that the following schedules were evaluated: ID\ID (N=2 454), IM\ID (N=511), and IM\IM (N=511).

Baseline data

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GID15: At inclusion, in the PPI population, subjects were aged between 18.1 and 58.0 years old and the mean age was 40.2 years (SD: 11.1 years). The male/female gender ratio was 0.6, the number of females was higher than the number of males in both groups. Both groups were similar in terms of age and gender distribution. The baseline characteristics (in terms of age, gender and previous influenza vaccination) were similar in the FASI and in the SafAS populations.

Among the 760 subjects included in the PPI population, 292 subjects (38.4%) had been vaccinated with an influenza vaccine in majority in 2004. Out of these 292 subjects, 33 (11.3%) had experienced an adverse reaction after vaccination with almost the same proportions in both groups. These reactions were nearly the same as the solicited reactions pre-listed in the subject's DC. Similar results were obtained in the FASI population.

GID23: At inclusion, in the PPI population, subjects were aged from 18.1 to 60.0 years and the mean age was 42.8 years (SD: 12.4 years). The male/female gender ratio was 0.7, the number of females being higher than the number of males in all groups. Among the 1 676 subjects included in the PPI population, 781 (46.6%) had been previously vaccinated with an influenza vaccine. Most of them had been vaccinated in 2005. Out of these 781 subjects, 56 (7.2%) had experienced an adverse reaction after vaccination (between 10 and 16 subjects per group). A total of 717 subjects (42.8%) were considered as at health risk. The most important risks were lung disease (15.2%), heart disease (13.7%) and neurological disease (13.6%). The majority of subjects had skin phototypes Type III (32.8%) or Type II (25.8%).

Baseline characteristics (in terms of age, gender, BMI, previous allergy, risk status, skin phototypes and previous influenza vaccination) were similar in the four groups, in the PPI, in the FASI, and in the SafAS populations.

GID16 At inclusion, in the PPI population, subjects were aged from 60.0 to 85.8 years and the mean age varied from 70.4 to 71.0 years (SD of 6.76 and 6.55 years, respectively). The male/female gender ratios varied from 0.8 to 1, the number of females being higher than the number of males in all three groups. All three groups were similar in terms of age and gender distribution.
Among the 1,076 subjects included in the PPI population, 978 had been previously vaccinated with an influenza vaccine.

GID17: At inclusion, the mean age of subjects in the FASI population was 70.8 years (SD: 6.8 years, range 60.6; 94.6). The male/female sex ratio was 0.8. Both groups were similar in terms of age and gender distribution. Distribution of BMI was similar amongst groups. Most of the subjects were overweight (44.2%) or obese (23.2%).

Among the 3 685 subjects included in the FASI population, a total of 2 924 subjects (79.3%) had been vaccinated with an influenza vaccine and 259 subjects (7.0%) with a pneumoccocal vaccine. Out of these subjects, 57 (1.9%) and none (0%) reported experiencing an adverse reaction after vaccination with influenza and pneumoccocal vaccines respectively.

With respect to the health risk status (65.6% in ID 15µg group and 63.6% in IM 15µg group) of the subjects included in the FASI population, heart disease was the most frequently medical condition reported (1892 subjects [51.3%]). Lung disease and diabetes were recorded for 428 subjects (11.6%) and 417 subjects (11.3%), respectively. Neurological disease was reported by 329 subjects (8.9%), and renal disease was reported by 186 subjects (5.0%). Other diseases, including hepatitis, cancer and leukemia were reported by 139 subjects (3.8%).

The baseline characteristics were equivalently distributed between groups, and were similar in the PPI and in the SafAS populations.

Outcomes and estimation

Immunogenicity results

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GID15
Pre-vaccination GMTs for each strain were similar in both groups. In the PPI, non-inferiority of the immunogenicity of the ID Influenza Vaccine 9µg to the IM Influenza Vaccine was demonstrated for each of the three strains in terms of post-vaccination GMTs, with the lower bound of difference of GMTs between groups ranging from -0.003 for the B strain to 0.087 for the A/H3N2 strain (Table 1). As non-inferiority was demonstrated, superiority of the ID Influenza Vaccine 9µg over the IM Influenza Vaccine was assessed. Superiority was shown for the A/H1N1 and the A/H3N2 strains but not for the B strain.

In the FASI, superiority of the ID Influenza Vaccine 9µg over the IM Influenza Vaccine was demonstrated for the A/H1N1 and the A/H3N2 strains, with lower bounds of difference of GMTs between groups of 0.006 and 0.087, respectively, but not for the B strain, for which the lower bound was of -0.004. However, post-vaccination GMTs for the B strain were still slightly higher in the ID 9µg group than in the IM group.

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Table 1: GID15 – Vac 1 - CPMP Immunogenicity Parameters, of the Three Vaccine Strains According to Injected Vaccine Group - Other Immunogenicity Analysis Set

		ID Influenza Vaccine 9µg			IM Influenza Vaccine		
Strain	**CPMP threshold**	**A/New Caledonia/20/99 (H1N1)**	**A/Wellington/1/2004 (H3N2)**	**B/Jiangsu/361/2002**	**A/New Caledonia/20/99 (H1N1)**	**A/Wellington/1/2004 (H3N2)**	**B/Jiangsu/361/2002**
N analyzed		382	383	382	385	384	385
PRE-VACCINATION							
Geometric mean (1/dil) (95% CI)		15.2 (13.2; 17.6)	29.3 (25.6; 33.5)	12.0 (10.8; 13.3)	14.4 (12.6; 16.5)	27.5 (24.3; 31.2)	11.4 (10.4; 12.6)
Seroprotection (≥ 40 [1/dil])							
% (95% CI)		27.7 (23.3; 32.5)	43.9 (38.8; 49.0)	16.8 (13.1; 20.9)	26.2 (21.9; 30.9)	40.9 (35.9; 46.0)	16.6 (13.0; 20.7)
POST-VACCINATION							
Geometric mean (1/dil) (95% CI)		247 (215; 285)	825 (736; 924)	144 (129; 161)	198 (170; 231)	569 (501; 646)	124 (111; 139)
Seroprotection (≥ 40 [1/dil])							
% (95% CI)	**>70%**	**92.4** (89.3; 94.9)	**99.7** (98.6; 100.0)	**90.6** (87.2; 93.3)	**88.8** (85.3; 91.8)	**98.7** (97.0; 99.6)	**85.5** (81.5; 88.8)
POST/PRE							
Ratios of Titers (95% CI)	**>2.5**	**16.2** (13.7; 19.2)	**28.2** (23.7; 33.5)	**12.1** (10.5; 13.8)	**13.8** (11.6; 16.4)	**20.7** (17.5; 24.4)	**10.84** (9.56; 12.29)
Seroconversion or significant increase							
% (95% CI)	**>40%**	**74.3** (69.7; 78.7)	**85.1** (81.2; 88.5)	**76.4** (71.9; 80.6)	**70.4** (65.6; 74.9)	**79.2** (74.8; 83.1)	**73.5** (68.8; 77.8)

N: number of subjects analyzed

Mean data fulfilling the CPMP criteria are shown in bold

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The proportions of seroprotected subjects at baseline were similar between groups, ranging from 16.8% for the B strain to 43.9% for the A/H3N2 strain, and from 16.6% for the B strain to 40.9% for the A/H3N2 strain, in the ID 9µg and IM groups.

Twenty-one days after vaccination, an immune response was observed in both groups, with GMTs of 247 (1/dil), 825 (1/dil) and 144 (1/dil), for the A/H1N1, A/H3N2 and B strains, respectively in the ID 9µg group.

The three CPMP criteria were fulfilled with the ID Influenza Vaccine 9µg for the three strains, 95% CIs inclusive, with higher results in the ID 9µg group than in the IM group. As there were only 34 subjects receiving ID injection and presenting with vaccine leakage at the injection site, the assessment of immunogenicity in these subjects was not performed.

Exploratory analyses were performed to assess, on the immune response obtained after the first vaccination in both groups the influence of the baseline seroprotection, the centre and the vaccinator.
The centre and vaccinator effect were generally not significant. On the other side, the baseline seroprotection was always significant and influence the immune response in each vaccine group. Nevertheless, the vaccine effect (ID vaccine effect compared to IM vaccine effect) is independent from this covariate.

Antibody persistence
For the three strains, the antibody persistence for one year after vaccination presented a similar decrease over time of GMTs in the ID 9µg group to the IM 15µg group, despite a constant slight higher level of antibodies in the ID group versus IM group.

The decrease of GMTs between D21 and M12 were comparable between the ID and IM groups for the three strains at each time point (M3, M6 and M12). Similar observations can be performed in terms of seroprotection rates (≥40 1/dil) (Table 2). It seems to be that for the B strain the seroprotection decrease is slightly higher in ID 9µg group than in IM 15µg group.

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Table 2: Antibody persistence: Seroprotection rates before first vaccination and 21 days, 3, 6 and 12 months after vaccination according to randomized vaccine group – full analysis set - first vaccination

	ID 9µg			IM 15µg		
	A/New Caledonia/ 20/99 (H1N1)	A/Wellington/ 1/2004 (H3N2)	B/Jiangsu /10/2003	A/New Caledonia/ 20/99 (H1N1)	A/Wellington/ 1/2004 (H3N2)	B/Jiangsu /10/2003
V01 (D0)						
N analyzed	383	383	383	385	385	385
Subjects with titers >=40 l/dil.						
(%)	27.7%	43.9%	16.7%	26.2%	40.8%	16.6%
95% CI	(23.3;32.4)	(38.8;49.0)	(13.1;20.8)	(21.7;30.9)	(35.8;45.9)	(13.0;20.7)
V02 (D21)						
N analyzed	382	383	382	385	384	385
Subjects with titers >=40 l/dil.						
(%)	92.4%	99.7%	90.6%	88.8%	98.7%	85.5%
95% CI	(89.3;94.9)	(98.6;100.0)	(87.2;93.3)	(85.3;91.8)	(97.0;99.6)	(81.5;88.8)
V03 (M3)						
N analyzed	377	376	377	379	378	379
Subjects with titers >=40 l/dil.						
(%)	86.7%	98.9%	77.5%	81.3%	97.1%	72.6%
95% CI	(82.9;90.0)	(97.3;99.7)	(72.9;81.6)	(77.0;85.1)	(94.9;98.5)	(67.8;77.0)
V04 (M6)						
N analyzed	372	372	370	377	377	376
Subjects with titers >=40 l/dil.						
(%)	82.0%	97.8%	61.4%	75.9%	95.8%	65.7%
95% CI	(77.7;85.8)	(95.8;99.1)	(56.2;66.3)	(71.2;80.1)	(93.2;97.6)	(60.7;70.5)

(To be continued)

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	ID 9µg			IM 15µg		
	A/New Caledonia/ 20/99 (H1N1)	A/Wellington/ 1/2004 (H3N2)	B/Jiangsu /10/2003	A/New Caledonia/ 20/99 (H1N1)	A/Wellington/ 1/2004 (H3N2)	B/Jiangsu /10/2003
V05 (M12)						
N analyzed	346	346	347	350	350	350
Subjects with titers >=40 l/dil.						
(%)	68.2%	96.2%	49.9%	67.7%	89.1%	53.7%
95% CI	(63.0;73.1)	(93.7;98.0)	(44.5;55.2)	(62.5;72.6)	(85.4;92.2)	(48.3;59.0)

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The ID Influenza Vaccine 9µg was at least as immunogenic as the IM Influenza Vaccine in terms of post-vaccination GMTs. The immune response induced by the ID Influenza Vaccine 9µg was superior in terms of GMTs to the one induced by the IM Influenza Vaccine for the two A strains. For each of the three strains, the three CPMP criteria were met with the ID Influenza Vaccine 9µg. The antibody persistence pattern did not differ appreciably between the ID and IM groups.

GID23

Lot-to-lot consistency

Equivalence of the immune response of the three industrial lots was demonstrated for each of the three strains, the two-sided 90% CIs of the difference between lots were between -0.176 and 0.176 for each pair of lots and for each strain. The same conclusion can be drawn with a more stringent 95% CI (Table 3). The same conclusions could be drawn when analysing the FASI population.

Comparison to the IM administration

As lot-to-lot consistency had been established, the three ID 9µg groups (one for each lot) were pooled. Immunogenicity results of the ID 9 µg investigational vaccine were compared to those of the IM control group on each strain (A/H3N2, A/H1N1, and B) in terms of GM of post-vaccination titers observed at D21. In the PPI population, GMs of pre-vaccination titers were similar in both groups and for the three strains (although those corresponding to the A/H3N2 strain were higher than those of the other strains in both groups).

Non-inferiority of the immunogenicity of the ID Influenza Vaccine 9µg (pool of the three ID groups) to the IM Influenza Vaccine was demonstrated for each of the three strains in the PPI: the lower bound of the difference of log10 transformed post-vaccination GMTs ID 9µg group versus IM group was higher than -0.176 for all strains (ranging from -0.084 for the A/H1N1 strain to -0.059 for the A/H3N2 strain) (Table 4). These results were confirmed in the FASI population.

As non-inferiority was demonstrated, superiority of the ID Influenza Vaccine 9µg over the IM Influenza Vaccine was assessed in the FASI and PPI populations. Superiority of the immunogenicity of the ID Influenza Vaccine 9µg over the IM Influenza Vaccine was not reached for any of the three strains.

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Table 3: Immunogenicity Primary Criteria - Equivalence Among the Three ID Vaccine Lots - Per Protocol Analysis Set for Immunogenicity by Randomized Subjects

	ID 9µg Lot1			ID 9µg Lot2			ID 9µg Lot3		
	A/New Caledonia /20/99(H1N1)	A/Wisconsin 67/2005(H3N2)	B/Malaysia 25/06/2004	A/New Caledonia /20/99(H1N1)	A/Wisconsin 67/2005(H3N2)	B/Malaysia 25/06/2004	A/New Caledonia /20/99(H1N1)	A/Wisconsin 67/2005(H3N2)	B/Malaysia 25/06/2004
PRE-VACCINATION									
N analyzed	418	418	417	418	418	418	414	414	412
Titers									
Geometric mean	18.8	24.1	10.9	20.0	24.9	10.4	19.7	22.4	10.4
(95% CI)	(16.4; 21.5)	(20.9; 27.8)	(10.1; 11.9)	(17.3; 23.0)	(21.4; 29.0)	(9.62; 11.3)	(17.1; 22.8)	(19.5; 25.8)	(9.56; 11.3)
POST-VACCINATION									
N analyzed	420	420	420	418	419	419	414	414	414
Titers									
Geometric mean	186	269	67.6	183	298	75.4	176	268	62.4
(95% CI)	(162; 214)	(236; 307)	(61.0; 74.9)	(159; 211)	(260; 340)	(67.4; 84.3)	(152; 204)	(234; 308)	(55.8; 69.7)
Ratio lot 1 versus lot 2									
GMT lot 1 / GMT lot 2	1.014	0.904	0.897						
(90% CI) of the ratio	(0.861;1.197)	(0.771;1.059)	(0.791;1.019)						
Log difference lot 1 versus lot 2									
log10(GMT lot 1)-log10(GMT lot 2)	**0.006**	**-0.044**	**-0.047**						
(90% CI) of the difference	(-0.065; 0.078)	(-0.113; 0.025)	(-0.102; 0.008)						

(to be continued)

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	ID 9µg Lot1			ID 9µg Lot2			ID 9µg Lot3		
	A/New Caledonia /20/99(H1N1)	A/Wisconsin 67/2005(H3N2)	B/Malaysia 25/06/2004	A/New Caledonia /20/99(H1N1)	A/Wisconsin 67/2005(H3N2)	B/Malaysia 25/06/2004	A/New Caledonia /20/99(H1N1)	A/Wisconsin 67/2005(H3N2)	B/Malaysia 25/06/2004
Equivalence lot 1 & 2*	Yes	Yes	Yes						
(95% CI) of the difference	(-0.079; 0.092)	(-0.126; 0.038)	(-0.113; 0.018)						
Ratio lot 1 versus lot 3									
GMT lot 1 / GMT lot 3	1.054	1.003	1.084						
(90% CI) of the ratio	(0.889;1.247)	(0.855;1.175)	(0.955;1.230)						
Log difference lot 1 versus lot 3									
log10(GMT lot 1)-log10(GMT lot 3)	**0.023**	**0.001**	**0.035**						
(90% CI) of the difference	(-0.051; 0.096)	(-0.068; 0.070)	(-0.020; 0.090)						
Equivalence lot 1 & 3*	Yes	Yes	Yes						
(95% CI) of the difference	(-0.065; 0.110)	(-0.082; 0.084)	(-0.031; 0.100)						
Ratio lot 2 versus lot 3									
GMT lot 2 / GMT lot 3				1.032	1.109	1.208			
(90% CI) of the ratio				(0.877;1.230)	(0.944;1.303)	(1.059;1.377)			

* Equivalence among the three lots if for each pair of lots and for each strain, the two-sided 90% CI of the log difference of the geometric mean titers lies between -0.176 and 0.176.

(to be continued)

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	ID 9µg Lot1			ID 9µg Lot2			ID 9µg Lot3		
	A/New Caledonia /20/99(H1N1)	**A/Wisconsin 67/2005(H3N2)**	**B/Malaysia 25/06/2004**	**A/New Caledonia /20/99(H1N1)**	**A/Wisconsin 67/2005(H3N2)**	**B/Malaysia 25/06/2004**	**A/New Caledonia /20/99(H1N1)**	**A/Wisconsin 67/2005(H3N2)**	**B/Malaysia 25/06/2004**
Log difference lot 2 versus lot 3									
log10(GMT lot 2)-log10(GMT lot 3)				**0.017**	**0.045**	**0.082**			
(90% CI) of the difference				(-0.057; 0.090)	(-0.025; 0.115)	(0.025; 0.139)			
Equivalence lot 2 & 3*				Yes	Yes	Yes			
(95% CI) of the difference				(-0.071; 0.104)	(-0.038; 0.128)	(0.014; 0.150)			

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Table 4: Immunogenicity Secondary Criteria . Non-inferiority of ID 9µg versus IM 15µg Randomized Vaccine Group - Per Protocol Analysis Set for Immunogenicity

	ID 9µg Pooled Lots			IM 15µg		
	A/New Caledonia /20/99(H1N1)	A/Wisconsin 67/2005(H3N2)	B/Malaysia 25/06/2004	A/New Caledonia /20/99(H1N1)	A/Wisconsin 67/2005(H3N2)	B/Malaysia 25/06/2004
PRE-VACCINATION						
N analyzed	1250	1250	1247	421	421	421
Titers						
Geometric mean	19.5	23.8	10.6	19.2	24.1	10.4
(95% CI)	(18.0; 21.1)	(21.9; 25.8)	(10.1; 11.1)	(16.6; 22.3)	(20.9; 27.9)	(9.65; 11.3)
POST-VACCINATION						
N analyzed	1252	1253	1253	421	421	421
Titers						
Geometric mean	182	278	68.3	187	274	69.8
(95% CI)	(168; 197)	(257; 301)	(64.1; 72.7)	(162; 216)	(244; 309)	(62.7; 77.8)
Ratio versus IM 15µg						
GMT ID / GMT IM	0.971	1.015	0.978			
(95% CI) of the ratio	(0.824;1.146)	(0.873;1.180)	(0.863;1.107)			

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	ID 9µg Pooled Lots			IM 15µg		
	A/New Caledonia /20/99(H1N1)	**A/Wisconsin 67/2005(H3N2)**	**B/Malaysia 25/06/2004**	**A/New Caledonia /20/99(H1N1)**	**A/Wisconsin 67/2005(H3N2)**	**B/Malaysia 25/06/2004**
Log difference versus IM 15µg						
log10(GMT ID)-log10(GMT IM)	-0.013	0.006	-0.01			
(95% CI) of the difference	(-0.084; 0.059)	(-0.059; 0.072)	(-0.064; 0.044)			
Non-inferiority*	Yes	Yes	Yes			
Superiority†	No	No	No			

* Non-inferiority if for each strain, the two-sided 95% CI of the log difference of the geometric mean titers ID-IM lies above -0.176.

† Superiority if for at least two strains, the two-sided 95% CI of the log difference of the geometric mean titers ID-IM lies above 0.

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Table 5: GID23 - CPMP Immunogenicity Criteria of the Three Vaccine Strains According to Injected Vaccine Group - Other Immunogenicity Analysis Set

Injected Vaccine Group		ID Influenza Vaccine 9µg			IM Influenza Vaccine		
	CPMP criteria	A/New Caledonia /20/99(H1N1)	A/Wisconsin 67/2005(H3N2)	B/Malaysia /2506/2004	A/New Caledonia /20/99(H1N1)	A/Wisconsin 67/2005(H3N2)	B/Malaysia /2506/2004
N analyzed		1296	1297	1294	436	436	436
PRE-VACCINATION							
Geometric mean of titer (1/dil) (95%CI)		19.8 (18.3; 21.4)	24.1 (22.2; 26.2)	10.6 (10.1; 11.1)	19.1 (16.6; 22.1)	24.2 (21.0; 27.9)	10.4 (9.64; 11.2)
Seroprotection (≥ 40 [1/dil])							
% (95% CI)		32.4 (29.9; 35.0)	37.7 (35.1; 40.4)	10.4 (8.7; 12.1)	31.2 (26.9; 35.8)	38.1 (33.5; 42.8)	8.5 (6.0; 11.5)
POST-VACCINATION							
Geometric mean of titer (1/dil) (95%CI)		181 (168;197)	277 (257;299)	67.7 (63.7;72.0)	186 (161;214)	271 (241;306)	68.9 (61.9;76.8)
Seroprotection (≥ 40 [1/dil])							
% (95% CI)	**>70%**	**87.2** (85.2; 89.0)	**93.5** (92.0; 94.8)	**72.9** (70.4; 75.3)	**86.2** (82.6; 89.3)	**95.4** (93.0; 97.2)	**74.8** (70.4; 78.8)
POST/PRE							
Ratios of Titers							
Geometric mean (1/dil) (95% CI)	**>2.5**	**9.17** (8.33; 10.1)	**11.5** (10.4; 12.7)	**6.39** (5.96; 6.84)	**9.71** (8.19; 11.5)	**11.2** (9.58; 13.1)	**6.63** (5.90; 7.46)
Seroconversion or significant increase rate							
% (95% CI)	**>40%**	**57.5** (54.7; 60.2)	**66.5** (63.8; 69.0)	**56.**7 (54.0; 59.4)	**56.4** (51.6; 61.1)	**69.3** (64.7; 73.6)	**60.8** (56.0; 65.4)

N: number of subjects analyzed

Mean data fulfilling the CPMP criteria are shown in bold

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Table 5 presents the assessment of CPMP criteria and GMTs. Baseline seroprotection rates were similar between groups for each strain, and were slightly higher for the A/H3N2 strain than for the A/H1N1 and B strains.

After vaccination, an immune response was observed in the ID and IM groups, with GMTs of 181 (1/dil), 277 (1/dil) and 67.7 (1/dil), for the A/H1N1, A/H3N2 and B strains, respectively in the ID 9µg group. These GMTs were similar to those observed in the IM group. The three CPMP criteria were fulfilled with the ID Influenza Vaccine 9µg for each of the three strains, 95% CIs inclusive.

Effect of presence of wheal after injection
In the SafAS population, 46.7% of the subjects receiving the ID 9 µg vaccine presented a wheal at injection site. Geometric mean of titers ratios (GMTRs) and seroconversion or significant increase rates results were very similar in subjects presenting a wheal with respect to those without a wheal at injection site, for each of the three strains, as well as post-vaccination GMTs and seroprotection rates for the A/H3N2 and B strains. For the A/H1N1 strain, post-vaccination GMTs and seroprotection rates were slightly higher in subjects presenting a wheal at injection site. All three CPMP criteria were met in both groups and for each of the three strains.

Effect of presence of leakage at the injection site
In the FASI population, only 80 subjects (4.5%) vaccinated by ID route presented a leakage at the injection site. In the OI population, 59 subjects were assessed for the A/H1N1 and A/H3N2 strains, and 58 subjects for the B strain. Subjects presenting a leakage obtained slightly lower immunogenicity results than those without leakage. However for these subjects the three EMEA criteria were fulfilled for each strain, except seroprotection rate for the B strain: 57.9% [41.2; 81.5].

Influence of co-variates on post-vaccination titers
The influence of several covariates was explored separately on log10-transformed post-vaccination titers in the FASI population. Seroprotection status at baseline (categorized as <40 and ≥40 [1/dil]), previous influenza vaccination status, age (<40 years or >40 years), country, BMI and risk status (defined as any lung, heart, renal, neurological diseases, any diabetes, or any other significant history (such as HIV, cancers, Hepatitis [A, B, C], epilepsy, auto-immune diseases, blood disorders) were found to have a statistically significant effect on log10-transformed post-vaccination titers in each group. However, whatever the studied covariate, the differences between vaccine groups were not significantly different across the covariate categories and the same trends were observed in both vaccine groups.

Influence of risk status on immune responses
The immune responses in subjects at risk were consistently lower than in subjects not at risk, however, there are no consistent differences between the ID and IM administration routes in this study.

Elderly
GID16
Non inferiority of the ID 15 µg vaccine versus the IM15 µg vaccine
Results of this primary analysis are summarized in Table 6 for the PPI population. The immunogenicity results observed in the ID 15µg group were first compared to those in the IM 15µg group using a non-inferiority testing approach on each strain. For each strain, the primary parameter for non-inferiority was the difference of the log10 transformation of post-vaccination GMTs between the compared vaccine groups: $\log_{10}(GMT_{ID})$- $\log_{10}(GMT_{IM})$. The non-inferiority criteria was that $\log_{10}(GMT_{ID})$- $\log_{10}(GMT_{IM})$>-0.176, (equivalent to GMT_{IM}/GMT_{ID}<1.5).

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Table 6: Immunogenicity Primary Criteria. Non-inferiority of ID 15µg versus IM 15µg Injected Vaccine Groups - Per Protocol Analysis Set for Immunogenicity

	ID 15µg			IM 15µg		
	A/New Caledonia/20/99	A/Wellington/1/2004	B/Jiangsu/10/2003	A/New Caledonia/20/99	A/Wellington/1/2004	B/Jiangsu/10/2003
PRE-VACCINATION (D0)						
N analyzed	357	356	358	357	357	358
Titers						
Geometric mean	23.2	96.5	27.4	24.1	87.1	25.1
(95% CI)	(20.8; 26.0)	(83.5; 112)	(24.4; 30.7)	(21.6; 26.8)	(75.1; 101)	(22.5; 28.1)
POST-VACCINATION (D21)						
N analyzed	358	358	359	357	358	358
Titers						
Geometric mean	86.6	402	101	57.1	236	67.9
(95% CI)	(76.5; 98.1)	(355; 455)	(90.8; 113)	(51.2; 63.7)	(206; 271)	(60.7; 76.0)
Log titers difference vs 15µg IM						
log10(GMT ID)-log10(GMT IM)	0.181	0.231	0.174			
95% CI	(0.109; 0.252)	(0.152; 0.311)	(0.106; 0.242)			
Non-inferiority*	Yes	Yes	Yes			
Superiority†	Yes	Yes	Yes			
Adjusted p-value‡	<.0001	<.0001	<.0001			

*Non-inferiority if the left limit of the 95% CI >-0.176
†Superiority if the left limit of the 95% CI >0
‡Dunnett adjustment for multiple (2) group comparisons for each strain

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In the PPI population, the non-inferiority of the immunogenicity of the ID 15 µg vaccine versus that of the IM 15 µg vaccine was demonstrated for each of the three strains: the lower bound of the difference of log10-transformed post-vaccination GMTs was higher than -0.176 for all strains. The following ratios of GMTs (95%CI) versus the IM 15µg group were observed: 1.52 (1.29; 1.79) for the A/H1N1 strain, 1.70 (1.42; 2.05) for the A/H3N2 strain and 1.49 (1.28; 1.74) for the B strain. As non-inferiority was demonstrated, superiority of the ID 15 µg vaccine over the IM 15 µg vaccine was assessed.

The superiority of the immunogenicity of the ID 15 µg vaccine versus that of the IM 15 µg vaccine was demonstrated in the FASI population for the three strains as the lower bound of the difference of log10-transformed post-vaccination GMTs was greater than 0 (lower bounds of 0.102 for the B strain, 0.112 for the A/H1N1 strain, and 0.153 for the A/H3N2 strain, with adjusted p values <0.0001). The observed GMTs were significantly higher in the ID 15µg group than in the IM 15µg group. The following ratios of GMTs (95%CI) versus the IM 15µg group were observed: 1.52 (1.29; 1.79) for the A/H1N1 strain, 1.70 (1.42; 2.04) for the A/H3N2 strain and 1.48 (1.26; 1.73) for the B strain.

Results obtained in the FASI and in the PPI populations led to the same conclusions, i.e. non-inferiority and superiority of the ID 15 µg vaccine for the three strains.

Comparison between each of the two ID vaccines and the IM vaccine
The comparison between the immune responses of the ID 15 µg and ID 21 µg vaccines versus that of the IM 15 µg vaccine, demonstrated a significant superiority of the two ID dose levels over the IM 15 µg dose level on at least two strains for each CPMP criterion. The comparison between the two ID dose levels both in terms of CPMP criteria and GMTs did not show the superiority of the ID Influenza Vaccine 21µg over the ID Influenza Vaccine 15µg.

Leakage at the injection site
Twenty-four subjects (6.5%) presented a leakage in the ID 15µg group and 21 subjects (5.7%) presented a leakage in the ID 21µg group. Theoretically, leakage of vaccine from the injection site may result in lower dose of vaccine being delivered and subsequently a lower immunogenicity response could be seen in individuals with leakage. As leakage was observed in less than 15% of subjects, the potential effect of the presence of leakage at the injection site on the immunogenicity results was not statistically assessed. However, the immunogenicity of the two ID groups was compared again to the IM 15µg group, in subjects with no leakage on the skin after ID injection, and the results remain similar to those obtained on all subjects.

Cell-mediated immunity
The cellular responses against influenza were measured in 90 elderly subjects after one injection of ID influenza vaccine (either 15 or 21 µg HA/strain per 0.1 ml dose) or the Vaxigrip Flu IM vaccine (15 µg HA/strain per 0.5 ml dose). Antigenic *in vitro* re-stimulations were performed on purified frozen PBMC before and 21 days after vaccination with either killed split of live homologous or heterologous influenza viruses. Both CD4 and CD8 responses were monitored by 3 different techniques; 1) intracellular IFN-γ and IL-4 staining by flow cytometry, 2) IL-2 release by ELISPOT and 3) Th1/Th2 cytokine profile /IL-4, IL-5, IL-10, IFN-γ, TNF-α, IL-2) by Cytometric Bead Array.

Before vaccination, an influenza-specific CD4 Th1 response was observed in all subjects, as judged by a predominant IFN-γ and IL-2 secretion and the absence of IL-4, IL-5 and IL-10 detection. This response detected before vaccination was only moderately increased by the vaccination and no significant difference was demonstrated between IM and ID routes on DC4 T-cell activation. A CD4 response against heterologous strains probably due to recognition of conserved CD4 epitope was observed pre and post vaccination, but once again, no significant difference was observed between ID and IM immunization routes.

A weak and heterogenous CD8 response was measured by ICS before and after vaccination. This response was not increased by the vaccination whatever the virus strain used for the in vitro re-stimulation. No significant differences could be demonstrated between IM and ID routes on CD8 T cell activation.

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In conclusion, this study showed that, in elderly population, 21 days after vaccination, the ID influenza vaccine, with a dosage equivalent or superior to that of Vaxigrip, induced a cellular response of comparable profile and intensity that the Vaxigrip administered by the IM route.

GID17
First vaccination

Superiority analysis
Pre-vaccination GMTs and seroprotection rates for each strain were similar between groups. The primary objective was to demonstrate that the ID investigational vaccine induces a better immunogenicity than the IM control vaccine in terms of seroprotection rate after the first vaccination. A two-step approach was adopted. First, the non-inferiority of the ID investigational vaccine was assessed based on the analysis performed on the PPI population. As a second step, superiority of the ID investigational vaccine was assessed, using the FASI population. These analyses are summarised in Table 7.

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Table 7: Immunogenicity Primary Criteria . Superiority of ID 15µg versus IM 15µg Injected Vaccine Groups. First Vaccination

Injected Vaccine Group	ID 15µg			IM 15µg		
Strain	A/New Caledonia/20/99 (H1N1)	A/Wisconsin /67/2005 (H3N2)	B/Malaysia/2506/2004	A/New Caledonia/20/99 (H1N1)	A/Wisconsin /67/2005 (H3N2)	B/Malaysia/2506/2004
PRE-VACCINATION*						
N analyzed*	2600	2600	2597	1077	1076	1077
Titers (1/dil)*						
Geometric mean	20.6	36.3	11.0	21.7	33.8	11.5
95% CI	(19.7 ; 21.5)	(34.2 ; 38.6)	(10.7 ; 11.4)	(20.2 ; 23.3)	(30.8 ; 37.2)	(10.9 ; 12.1)
POST-VACCINATION*						
N analyzed*	2595	2595	2592	1077	1078	1078
Titers (1/dil)*						
Geometric mean	81.9	298	39.9	69.1	181	34.9
95% CI	(78.2 ; 85.8)	(282 ; 315)	(38.2 ; 41.6)	(64.1 ; 74.4)	(167 ; 197)	(32.7 ; 37.3)
Ratio vs. IM 15µg†						
GMT_{ID}/GMT_{IM}	1.190	1.641	1.143			
(95% CI) of the ratio	(1.091 ;1.300)	(1.483 ;1.816)	(1.062 ;1.242)			
Log difference vs. IM 15µg†						
$log10(GMT_{ID})-log10(GMT_{IM})$	0.076	0.215	0.06			
(95% CI) of the difference	(0.038 ; 0.114)	(0.171 ; 0.259)	(0.026 ; 0.094)			
Non-inferiority	Yes	Yes	Yes			
Seroprotection (>= 40 l/dil)‡						
n/N	1998/2595	2422/2595	1443/2592	767/1077	947/1078	529/1078
%	77.0	93.3	55.7	71.2	87.8	49.1
Difference vs. IM 15µg	5.78	5.49	6.60	-	-	-
(95%CI) of the difference	(2.67 ; 8.97)	(3.40 ; 7.76)	(3.05 ; 10.1)	-	-	-
Superiority*	Yes	Yes	Yes	-	-	-

* FASI population results

† PPI results: Non-inferiority if for each strain, the two-sided 95% CI of the log difference of the geometric mean titers ID-IM lies above -0.176.

‡ FASI results: Superiority if for at least two strains, the two-sided 95% CI of the difference of the seroprotection rate ID-IM lies above 0.

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As non-inferiority was demonstrated, superiority of the ID 15 µg vaccine over the IM 15 µg vaccine was assessed in the FASI population. The superiority of the immunogenicity of the ID 15 µg vaccine versus that of the IM 15 µg vaccine was demonstrated in the FASI population for the three strains as the lower bound of the 95% CI of the difference of the seroprotection rates (ID - IM) was above zero (lower bound of 2.67 for the A/H1N1 strain, 3.40 for the A/H3N2 strain and 3.05 for the B strain). The point estimates for the differences of seroprotection rates between the two groups (ID 15 µg . IM 15 µg) were 5.78 for the A/H1N1 strain, 5.49 for the A/H3N2 strain and 6.60 for the B strain.

Results obtained in the FASI and in the PPI populations led to the same conclusions; respectively, non-inferiority of the ID 15 µg vaccine versus the IM 15 µg vaccine in terms of GMTs for the three strains, and superiority of the ID 15 µg vaccine over the IM 15 µg vaccine in terms of seroprotection rates for the three strains.

CPMP criteria
Overall, seroprotection rates obtained met the CPMP requirements, in both groups, for the A/H1N1 and A/H3N2 strains, values obtained for these two strains being >60%, 95% CIs inclusive. In terms of GMTRs, this CPMP criteria is met for all strains in both groups, 95% CIs inclusive. Seroconversion rates or significant increase in titers obtained meet the CPMP requirements for all strains in the ID 15µg group (95% Cis inclusive), and for the A/H3N2 and B strains in the IM 15µg group.

Table 8 presents the assessment of the CPMP criteria and GMTs.

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Table 8: GID17 Vac1 - CPMP Immunogenicity Parameters of the Three Vaccine Strains According to Injected Vaccine Group - Subjects with Pre- and Post-vaccination Titers – Other Immunogenicity Analysis Set

		ID Influenza Vaccine 15µg			**IM Influenza Vaccine**		
Strain	**CPMP threshold**	A/New Caledonia /20/99(H1N1)	A/Wisconsin 67/2005(H3N2)	B/Malaysia /2506/2004	A/New Caledonia /20/99(H1N1)	A/Wisconsin 67/2005(H3N2)	B/Malaysia /2506/2004
N analyzed		2585	2586	2582	1076	1075	1077
PRE-VACCINATION							
Geometric mean (1/dil) (95% CI)		20.6 (19.7; 21.5)	36.3 (34.2; 38.6)	11.0 (10.7; 11.4)	21.6 (20.1; 23.2)	33.9 (30.8; 37.2)	11.5 *(10.9; 12.1)*
Seroprotection (≥ 40 [1/dil])							
% (95% CI)		32.5 (30.7; 34.3)	48.9 (47.0; 50.9)	12.0 (10.7; 13.3)	33.8 (31.0; 36.7)	47.0 (44.0; 50.0)	12.4 *(10.5; 14.6)*
POST-VACCINATION							
N analyzed		2585	2586	2582	1076	1075	1077
Geometric mean (1/dil) (95% CI)		81.7 (78.0;85.6)	298 (282;315)	39.9 (38.3;41.6)	68.8 (63.8; 74.2)	181 (167;197)	34.8 *(32.6;37.2)*
Seroprotection (≥ 40 [1/dil])							
% (95% CI)	**>60%**	**77.0** (75.3; 78.6)	**93.3** (92.3; 94.3)	55.7 (53.8; 57.6)	**71.1** (68.3; 73.8)	**87.9** (85.8; 89.8)	48.9 *(45.9; 52.0)*
POST/PRE							
Ratios of Titers (95% CI)	**>2**	**3.97** (3.77; 4.18)	**8.19** (7.68; 8.74)	**3.61** (3.47; 3.76)	**3.19** (2.94; 3.45)	**5.35** (4.87; 5.88)	**3.04** *(2.85; 3.24)*
Seroconversion or significant increase							
% (95% CI)	**>30%**	**38.7** (36.8; 40.6)	**61.3** (59.3; 63.1)	**36.4** (34.5; 38.3)	30.0 (27.3; 32.9)	**46.9** (43.9; 49.9)	**30.7** *(28.0; 33.6)*

N: number of subjects analyzed

Mean data fulfilling the CPMP criteria are shown in bold

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Table 9: GID17 Vac2 - EMEA Immunogenicity Parameters of the Three Vaccine Strains According to Injected Vaccine Group - Subjects with Pre- and Post-vaccination Titers - Other Immunogenicity Analysis Set

		ID Influenza Vaccine 15µg			IM Influenza Vaccine		
Strain	**EMEA threshold**	**A/Solomon Islands/3/2006 (H1N1)**	**A/Wisconsin /67/2005 (H3N2)**	**B/Malaysia/2506/2004**	**A/ Solomon Islands/3/2006 (H1N1)**	**A/Wisconsin /67/2005 (H3N2)**	**B/Malaysia/2506/2004**
N analyzed		261	259	262	143	142	143
PRE-VACCINATION							
Geometric mean (1/dil) (95% CI)		20.8 (18.2; 23.7)	112 (94.4; 132)	24.3 (21.6; 27.3)	19.0 (15.6; 23.0)	102 (81.8; 127)	22.4 (19.3; 25.9)
Seroprotection (≥ 40 [1/dil])							
% (95% CI)		29.1 (23.7; 35.0)	80.3 (74.9; 85.0)	34.4 (28.6; 40.4)	25.9 (18.9; 33.9)	80.3 (72.8; 86.5)	35.0 (27.2; 43.4)
POST-VACCINATION							
N analyzed		261	259	262	143	142	143
Geometric mean (1/dil) (95% CI)		204 (175; 239)	382 (334; 438)	46.2 (41.4; 51.6)	137 (108; 175)	293 (240; 357)	37.4 (32.0; 43.7)
Seroprotection (≥ 40 [1/dil])							
% (95% CI)	**>60%**	**93.1** (89.3; 95.9)	**98.1** (95.6; 99.4)	59.9 (53.7; 65.9)	**81.8** (74.5; 87.8)	**95.8** (91.0; 98.4)	53.1 (44.6; 61.5)
POST/PRE							
Ratios of Titers (95% CI)	**>2**	**9.84** (8.43; 11.5)	**3.42** (2.99; 3.91)	1.90 (1.75; 2.07)	**7.24** (5.82; 9.02)	**2.88** (2.43; 3.41)	1.67 (1.50; 1.86)
Seroconversion or significant increase							
% (95% CI)	**>30%**	**76.2** (70.9; 81.3)	**45.9** (39.8; 52.2)	17.2 (12.8; 22.3)	**63.6** (55.2; 71.5)	**40.1** (32.0; 48.7)	9.8 (5.5; 15.9)

N: number of subjects analyzed

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Second vaccination

Immunogenicity results after Vac2 are presented (Table 9) in the Other Immunogenicity Analysis Set population. Prevaccination GMTs for each strain were similar between groups. The proportions of seroprotected subjects at baseline were similar between the ID 15µg and IM groups.

Data are not yet available for Vac3. The interim iCSR including results obtained up to 21 days after Vac3 will be available in May 2009.

Based on the results after Vac2, it is expected that the same trend will be obtained after Vac3, confirming acceptable repeatability of ID vaccination.

Antibody persistence
In GID17, 12 months after Vac1, the seroprotection rates decreased over time with a similar trend observed for the ID Influenza Vaccine 15µg and the IM Influenza Vaccine for the three strains. At D180 and D365, seroprotection rates remained slightly higher to similar in the ID 15µg and IM 15µg groups for the A/H1N1 and the A/H3N2 strains. For the B strain, at D180 and D365, the seroprotection rates were slightly lower to similar in the ID 15µg and IM 15µg groups (30.5% at D180 and D365 in the ID 15µg group versus 34.0% and 38.3% at D180 and D365, respectively, in the IM 15µg group).

In both groups, antibody titers remained higher than pre-vaccination titers 12 months after Vac1. At D90 and D180, the seroprotection rate remained ≥ 60% in the ID 15µg and IM 15µg group for the A strains, except for the A/H1N1 strain in the IM 15µg group at D180. At D365, the seroprotection rate remained ≥ 60% in both groups for the A/H3N2 strain, but not for the A/H1N1 and the B strains.

As regards GMTs, they remained slightly higher in the ID 15µg group than in the IM 15µg group for the A/H3N2 strain until D365. For the A/H1N1 strain, anti-HA antibodies remained higher in the ID 15µg group than in the IM 15µg group until D90, and were similar at D180 and D365.

For the B strain, the antibody persistence curve was similar to the A strains although titers were lower.

There were no major differences between the ID Influenza Vaccine 15µg and the IM Influenza Vaccine regarding the drop in GMTs, i.e. ratios of GMTs V03/V02, V04/V02, and V05/V02 for any strain.

Effect of presence of wheal or after injection or presence of leakage at the injection site
Among the subjects vaccinated with the ID 15 µg vaccine, 1 149 (44.1%) presented a wheal at the injection site. In the OI analysis set, no difference was observed in the immune response between subjects presenting a wheal or not at injection. The immune response in these subsets of subjects was similar to the one observed in the whole population

Analysis of immunogenicity parameters (post-vaccination GMTs and CPMP criteria) was conducted on subgroups of subjects of the ID 15µg group (OI population) presenting (or not) a leakage of the vaccine product after injection. Among the subjects vaccinated with the ID 15 µg vaccine, 65 (2.5%) presented a leakage, and 2 539 (97.4%) had no leakage. All parameters presented showed no relevant differences between subjects presenting a leakage and those without leakage

Baseline seroprotection status
The post-vaccination GMTs and GMTRs were described in the FASI population in the subjects who were not seroprotected at baseline (titer <40 [1/dil]). A large number of subjects were not seroprotected before vaccination: 1 749 (66.3%) and 711 subjects (57.0%), (A/H1N1 strain), in the ID 15µg and IM 15µg groups, respectively, 1 325 (87.0%) and 570 (77.4%) (A/H3N2 strain), and 2 280 (49.9%) and 942 (42.6%) (B strain).

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Among these subjects, post-vaccination seroprotection rates were higher for subjects vaccinated with the ID 15 µg vaccine than for those vaccinated with the IM 15 µg vaccine. Indeed, the differences in seroprotection rates (ID-IM) and 95% CI were of 9.36% (5.12; 13.6) for the A/H1N1 strain, 9.65% (5.88; 13.6) for the A/H3N2 strain and 7.34% (3.56; 11.1) for the B strain. The responses were consistently lower in subjects with a baseline titer<40 [1/dil], than in subjects who were seroprotected at baseline.

Influence of potentially important covariates on seroprotection rates at D21
Additionally, the influence of several covariates (previous influenza vaccination status, gender, age group, country, BMI and risk status) on seroprotection rates observed in the ID 15µg and IM 15µg groups were explored separately in the FASI population. Whatever the studied covariate, the odds ratio between vaccine groups was not significantly different across the covariate categories and the same trends were observed in both vaccine groups.

- Clinical studies in special populations

No studies in special populations were performed.

- Analysis performed across trials (pooled analyses and meta-analysis)

An integrated analysis of study GID15 and GID23 was performed. The analysis provides a descriptive comparison between the ID 9µg and IM 15 µg vaccines. The results of the analysis did not change the conclusions from each individual study.

An integrated analysis of studies GID16 and GID17 was performed. The analysis provides a descriptive comparison of between the ID 15µg and IM 15 µg vaccines. The results of the analysis did not change the conclusions from each individual study.

Clinical safety

- Patient exposure

The overall safety analysis set across all the studies of the clinical development program, regardless of the delivery system used, included 3 994 vaccinations for the ID Influenza Vaccine 9µg and 3 031 vaccinations for the ID Influenza Vaccine 15µg.

Pooled data from the four key trials represent a total of 2384 adult subjects administered ID Influenza Vaccine 9µg and 2974 elderly subjects administered ID Influenza Vaccine 15µg. Comparison is made with 843 and 1458 subjects, respectively, having received IM Influenza Vaccine as a comparator.

The demographic characteristics at baseline were homogeneous between the key studies and between the groups of each individual study. In the adult indication fewer males than females were included in these studies: 40.9% versus 59.1% in the ID 9µg group and 39.1% versus 60.9% in the IM 15µg group. Baseline parameters such as skin type, body mass index (BMI), and risk status were measured in GID23 and were homogeneous between the ID 9µg and IM 15µg groups.

Fewer males than females were included in the key elderly studies: 45.3% versus 54.7% in the ID 15µg group and 46.3% versus 53.7% in the IM 15µg group. Baseline parameters such as skin type, BMI, and risk status were measured in GID17 and were homogeneous between the ID 15µg and IM 15µg groups.

- Adverse events

Table 10 presents an overall summary of solicited and unsolicited reactions and events and SAEs 21 days post-vaccination in the key studies in adults and in the elderly. As shown in this overview table, the frequency of injection site reactions was expectedly higher in subjects vaccinated by the ID route than by the IM route. Moreover, no difference emerged between the ID and the IM group in terms of

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solicited systemic AEs and unsolicited AEs. In terms of age group, AEs and reactions tended to be more frequent in adults than in the elderly overall.

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Table 10: Key Studies – Adults and Elderly – Summary of Adverse Events and Reactions within 21 Days after Vaccination (Safety Analysis Set)

	ADULTS						ELDERLY					
	Overall ID 9µg (N=2384)			Overall IM 15µg (N=843)			Overall ID 15µg (N=2974)			Overall IM 15µg (N=1458)		
	n/M	%	95% CI	n/M	%	95% CI	n/M	%	95% CI	n/M	%	95% CI
SUBJECTS WITH AT LEAST ONE:												
- Solicited injection site reaction	2185/2356	92.7	(91.6; 93.8)	485/829	58.5	(55.1; 61.9)	2353/2965	79.4	(77.9; 80.8)	491/1451	33.8	(31.4; 36.3)
- Severe solicited injection site reaction	452/2356	19.2	(17.6; 20.8)	34/829	4.1	(2.9; 5.7)	469/2965	15.8	(14.5; 17.2)	42/1451	2.9	(2.1; 3.9)
- Solicited systemic reaction	1050/2356	44.6	(42.5; 46.6)	404/829	48.7	(45.3; 52.2)	726/2965	24.5	(22.9; 26.1)	351/1451	24.2	(22.0; 26.5)
- Moderate or severe solicited systemic reaction	320/2356	13.6	(12.2; 15.0)	108/829	13.0	(10.8; 15.5)	142/2965	4.8	(4.0; 5.6)	79/1451	5.4	(4.3; 6.7)
- Severe solicited systemic reaction	65/2356	2.8	(2.1; 3.5)	25/829	3.0	(2.0; 4.4)	40/2965	1.3	(1.0; 1.8)	22/1451	1.5	(1.0; 2.3)
- Unsolicited event	617/2357	26.2	(24.4; 28.0)	225/830	27.1	(24.1; 30.3)	338/2966	11.4	(10.3; 12.6)	150/1451	10.3	(8.8; 12.0)
- Severe unsolicited event	52/2357	2.2	(1.7; 2.9)	22/830	2.7	(1.7; 4.0)	28/2966	0.9	(0.6; 1.4)	7/1451	0.5	(0.2; 1.0)
- Unsolicited systemic event	594/2357	25.2	(23.5; 27.0)	218/830	26.3	(23.3; 29.4)	329/2966	11.1	(10.0; 12.3)	146/1451	10.1	(8.6; 11.7)

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	ADULTS						ELDERLY					
	Overall ID 9µg (N=2384)			Overall IM 15µg (N=843)			Overall ID 15µg (N=2974)			Overall IM 15µg (N=1458)		
	n/M	%	95% CI	n/M	%	95% CI	n/M	%	95% CI	n/M	%	95% CI
- Moderate or severe unsolicited systemic event	240/2357	10.2	(9.0; 11.5)	84/830	10.1	(8.2; 12.4)	138/2966	4.7	(3.9; 5.5)	65/1451	4.5	(3.5; 5.7)
- Severe unsolicited systemic event	48/2357	2.0	(1.5; 2.7)	22/830	2.7	(1.7; 4.0)	28/2966	0.9	(0.6; 1.4)	7/1451	0.5	(0.2; 1.0)
- Unsolicited reaction	161/2357	6.8	(5.8; 7.9)	57/830	6.9	(5.2; 8.8)	60/2966	2.0	(1.5; 2.6)	28/1451	1.9	(1.3; 2.8)
- Severe unsolicited reaction	15/2357	0.6	(0.4; 1.0)	5/830	0.6	(0.2; 1.4)	4/2966	0.1	(0.0; 0.3)	2/1451	0.1	(0.0; 0.5)
- Unsolicited injection site reaction	41/2357	1.7	(1.3; 2.4)	12/830	1.4	(0.7; 2.5)	13/2966	0.4	(0.2; 0.7)	5/1451	0.3	(0.1; 0.8)
- Severe unsolicited injection site reaction	4/2357	0.2	(0.0; 0.4)	0/830	0.0	(0.0; 0.4)	0/2966	0.0	(0.0; 0.1)	0/1451	0.0	(0.0; 0.3)
- Unsolicited systemic reaction	124/2357	5.3	(4.4; 6.2)	46/830	5.5	(4.1; 7.3)	50/2966	1.7	(1.3; 2.2)	23/1451	1.6	(1.0; 2.4)
- Moderate or severe unsolicited systemic reaction	42/2357	1.8	(1.3; 2.4)	16/830	1.9	(1.1; 3.1)	26/2966	0.9	(0.6; 1.3)	8/1451	0.6	(0.2; 1.1)
- Severe unsolicited systemic reaction	11/2357	0.5	(0.2; 0.8)	5/830	0.6	(0.2; 1.4)	4/2966	0.1	(0.0; 0.3)	2/1451	0.1	(0.0; 0.5)

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	ADULTS						ELDERLY					
	Overall ID 9µg (N=2384)			**Overall IM 15µg (N=843)**			**Overall ID 15µg (N=2974)**			**Overall IM 15µg (N=1458)**		
	n/M	**%**	**95% CI**	**n/M**	**%**	**95% CI**	**n/M**	**%**	**95% CI**	**n/M**	**%**	**95% CI**
- Any SAE within 21 days	11/2384	0.5	(0.2; 0.8)	1/843	0.1	(0.0; 0.7)	20/2974	0.7	(0.4; 1.0)	9/1458	0.6	(0.3; 1.2)
- Any non-fatal SAE within 21 days	11/2384	0.5	(0.2; 0.8)	1/843	0.1	(0.0; 0.7)	19/2974	0.6	(0.4; 1.0)	9/1458	0.6	(0.3; 1.2)

Notes:

For solicited reactions, the denominator for percentages is the number of vaccinated subjects with at least one safety record available for solicited reactions. For unsolicited events, the denominator for percentages is the number of vaccinated subjects with at least one safety record available. For Serious Adverse Events, the denominator is the number of vaccinated subjects.

n: number of subjects

By convention for the integrated analysis, solicited AEs (at injection site or systemic) were considered as related to the vaccination and are called solicited injection site reactions or solicited systemic reactions.

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Results on key studies correspond only to the data of GID23 in adults and GID17 in the elderly.

Immediate reactions
In the key studies, few immediate reactions were reported overall and most were reported in adults. These reactions tended to occur in a similar proportion in the ID and IM group.

In the ID group, 11 adult subjects out of 1796 (0.6%) had 16 immediate reactions and three elderly subjects out of 2612 (0.1%) had four immediate reactions. In the IM group, two adult subjects out of 453 (0.4%) had two immediate reactions; none occurred in the elderly. None of the subjects with at least one immediate reaction had a SAE.

In the adult and in the elderly population, immediate reactions in the ID group occurred mostly in the System Organ Class (SOC) of Nervous System Disorders (five reactions in five subjects), Gastro-Intestinal Disorders (three reactions in three subjects), Infections and Infestations (two reactions in two subjects), General Disorders (two reactions in one subject), and Musculo-Skeletal Disorders (two reactions in two subjects).

All immediate reactions in the elderly were mild. In adults, most were mild. Four adult subjects experienced eight moderate or severe immediate reactions.

In the overall adult and elderly populations combined, 17 subjects out of 6537 vaccinations (0.3%) had 23 immediate reactions in the ID group and two subjects out of 3001 vaccinations (0.1%) had two immediate reactions in the IM group.

Solicited Reactions

By convention for the integrated analysis, solicited AEs, at injection site or systemic, were considered as related to the vaccination and are called solicited injection site reactions or solicited systemic reactions

Injection site reactions

In both the adult and elderly population, injection site reactions following ID vaccination with respect to IM injection were more frequent, as seen in the key trials. This was expected, and confirmed results obtained in the earlier trials. In the pool of all studies, the frequency of solicited injection site reactions was similar to what was observed in the key studies.

All solicited injection site reactions, with the exception of echymosis, were observed with incidences ≥ 10% in the ID Influenza Vaccine groups (both adult and elderly population). The injection site reactions erythema, swelling, induration were more frequent and more extensive in subjects vaccinated with the ID Influenza Vaccine with respect to the IM Influenza Vaccine. Pruritus was also more frequently reported following ID vaccination. The majority of the injection site reactions initially occurred the day following vaccination. Importantly, the majority lasted only 3 days and resolved spontaneously.

In terms of severity, a marked difference was observed for erythema, swelling and induration in favour of the IM group, especially for erythema, and tended to occur longer than in the subjects vaccinated by de IM route. In both the adult and the elderly population, solicited injection site reactions in the subjects vaccinated by the ID route were more frequent (especially erythema, induration, swelling and pruritus)

In both adults and elderly injection site pain, as well as injection site ecchymosis, whether severe or not, occurred in similar proportions in the IM and ID group

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Table 11: Incidences of Injection Site and Systemic Solicited Reactions after Vaccination with either ID Influenza Vaccine 9µg, ID Influenza Vaccine 15µg or IM Influenza Vaccine (Key studies)

Symptom	Grade	Adults				Elderly			
		9µg ID N = 2384		15µg IM N = 843		15µg ID N = 2974		15µg IM N = 1458	
		n	%	n	%	N	%	N	%
Injection site reactions (evaluated from Day 0 to Day 7 after vaccination)									
Injection site pain	Any	985	41.9	364	44.0	657	22.2	248	17.1
	Severe	3	0.1	1	0.1	5	0.2	0	0.0
Injection site erythema	Any	2002	85.0	157	19.0	2132	71.9	23[illegible]	16.1
	Severe	401	17.0	24	2.9	392	13.2	30	2.1
Injection site swelling	Any	1474	62.7	123	14.9	1157	39.0	140	9.7
	Severe	147	6.3	13	1.6	117	3.9	16	1.1
Injection site induration	Any	1445	61.5	165	19.9	1214	40.9	183	12.6
	Severe	104	4.4	9	1.1	66	2.2	13	0.9
Injection site ecchymosis	Any	195	8.3	54	6.5	128	4.3	61	4.2
	Severe	12	0.5	3	0.4	12	0.4	3	0.2
Injection site pruritus	Any	1005	42.7	75	9.1	867	29.2	98	6.8
	Severe	9	0.4	1	0.1	10	0.3	1	0.1
Systemic reactions (evaluated from Day 0 to Day 21 after vaccination)									
Fever	Any	89	3.8	29	3.5	72	2.4	51	3.5
	Moderate/severe	18	0.8	6	0.7	14	0.5	8	0.6
Headache	Any	709	30.2	249	30.1	405	13.7	202	13.9
	Moderate/Severe	191	8.1	70	8.5	69	2.3	32	2.2
Malaise	*Any*	*407*	*17.3*	*152*	*18.4*	*268*	*9.0*	*122*	*8.4*
	Moderate/Severe	*127*	*5.4*	*50*	*6.0*	*59*	*2.0*	*33*	*2.3*
Myalgia	*Any*	*531*	*22.6*	*244*	*29.5*	*321*	*10.8*	*163*	*11.2*
	Moderate/Severe	*110*	*4.7*	*41*	*5.0*	*64*	*2.2*	*40*	*2.8*
Shivering	*Any*	*205*	*8.7*	*66*	*8.0*	*122*	*4.1*	*69*	*4.8*
	Moderate/Severe	*47*	*2.0*	*14*	*1.7*	*22*	*0.7*	*9*	*0.6*

Systemic reactions

In adults and in the elderly, *headache, malaise*, and *myalgia* were the most commonly reported solicited reactions.In both the adult and the elderly population, solicited systemic reactions were found to occur with the same frequency in the subjects vaccinated by the ID route or by the IM route.

Solicited systemic reactions were not found either to be more severe or to occur longer in the ID group than in the subjects vaccinated by the IM route. Except for three reactions that were not solicited in the key studies, i.e. *asthenia, arthralgia*, and *sweating*, no difference emerged from the analysis of solicited systemic reactions in the pool of all studies compared to the key studies. There was no safety signal as regards the solicited systemic reactions that occurred within 7 days after vaccination, whatever the dose level of ID Influenza Vaccine and the delivery route

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Overall the systemic solicited reactions were more frequent in the adult than in the elderly population. Data from the key studies confirm that the incidences of systemic reactions were similar following ID administration with respect to IM administration in both the adults and the elderly population (Table 11).

CHMP immunogenicity criteria for influenza vaccines

In both the adults and the elderly population, EMEA-defined reactions occurred at similar frequencies following ID or IM administration in the key studies. The most frequently reported reactions in both groups were malaise, shivering, and injection site ecchymosis.

Unsolicited adverse events

Unsolicited events reported for approximately 21 days after vaccination were analyzed across key studies, first by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC), then by primary Preferred Term (PT). Unsolicited AEs occurring at injection site are considered as reactions.

Approximately 75% of the events reported were considered as unrelated to vaccination by the study investigators. The frequencies of all reactions by SOC were <3% for adults administered ID Influenza Vaccine 9µg and < 1% for elderly subjects administered ID Influenza Vaccine 15µg. Analysis of SOCs corresponding to reported reactions showed no clinically relevant differences between the ID Influenza Vaccine and the IM vaccine in both adults and elderly. Each individual reaction was reported at a frequency below 1%.

Adult Studies

In the **key studies**, the most common unsolicited AEs and reactions occurred in the same SOCs in the ID and the IM group, although not in the same order of frequency. Overall frequencies were similar between the ID and the IM group, for each SOC and in terms of severity and relation to vaccination.

In the ID group, the SOCs with the highest frequencies of events and reactions were Infections and Infestations (9.3% - mostly nasopharyngitis and rhinitis), Nervous System Disorders (5.2% - mostly headache and migraine), General Disorders (4.2% - mostly fatigue, influenza-like illness, asthenia, and injection site warmth), Respiratory, Thoracic and Mediastinal Disorders (4.2% - mostly pharyngolaryngeal pain), Gastrointestinal Disorders (3.6% - mostly diarrhea and nausea), and Musculoskeletal and Connective Tissue Disorders (3.6% - mostly back pain, myalgia, arthralgia, pain in extremity). Similar results were found in the overall IM group.

The *AEs* categorized as common (i.e. with a frequency >1%) in the ID group were:

- Nasopharyngitis (3.9%)
- Headache (3.4%)
- Pharyngolaryngeal pain (2.6%)
- Rhinitis (1.4%)
- Back pain (1.3%)
- Cough (1.1%)
- Dysmenorrhea (1.1%)

In terms of severity, the highest proportion of subjects with unsolicited moderate or severe *AEs* occurred, in both the ID and the IM group, in the SOC of Infections and Infestations (3.1% of ID subjects).

No unsolicited adverse *reaction* was found to be common at the PT level in the key adult studies. Some systemic reactions appeared to be common at the SOC level (General Disorders and Administration Site Conditions, and Infections and Infestations). Those were never moderate or severe.

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In both the ID and the IM group, the highest proportion of subjects with moderate or severe unsolicited *reactions* was found in the SOC of General Disorders and Administration Site Conditions, with 0.5% to 0.6% (and in the SOC of Infections and Infestations in the IM group with 0.5%), including five cases of severe influenza-like illness (0.2%), three cases of severe asthenia (0.1%), and three cases of severe fatigue (0.1%). As for severe *injection site* reactions, they included one severe injection site discoloration, one severe injection site reaction, and one severe injection site warmth.

In the pool of **all studies**, the most frequent unsolicited events and reactions occurred in the same SOCs as in the key studies. Overall frequencies were similar between the ID and the IM group, for each SOC and in terms of relation to vaccination.

Elderly Studies

In the key studies, the most common unsolicited events and reactions occurred in the same SOCs in the ID and the IM group, although not in the same order of frequency. Overall frequencies were similar between the ID and the IM group, for each SOC and in terms of severity and relation to vaccination. In GID16, however, a higher proportion of subjects had unsolicited systemic AEs in the ID group (20.6%) than in the IM group (14.4%) overall, although similar frequencies were found at the level of each SOC individually.

In the ID group, the SOCs with the highest frequencies of events and reactions were Infections and Infestations (4.2%, mostly nasopharyngitis), Musculoskeletal and Connective Tissue Disorders (2.4%, mostly back pain), General Disorders and Administration Site Conditions (1.4%, mostly fatigue, pyrexia, and asthenia), Gastrointestinal Disorders (1.2%, mostly diarrhea), Respiratory, Thoracic and Mediastinal Disorders (1.2%, mostly pharyngolaryngeal pain and cough), Nervous System Disorders (0.9%, mostly headache and dizziness). Similar results were found in the overall IM group.

Nasopharyngitis was the only *AE* considered as common at the PT level (1.0% in the IM group, and 1.2% in the ID group). The SOCs with an overall ID frequency >1% were similar in the IM group. In the ID group, no moderate or severe systemic AE appeared to be common at the level of the PT, only at the level of the SOC: Infections and Infestations (1.6%) and Musculoskeletal and Connective Tissue Disorders (1.1%). No systemic or injection site reaction was found to be common at the PT level. Similar results were found in the overall IM group.

In terms of severity, the highest proportion of subjects with unsolicited moderate or severe *AEs* occurred, in the ID and the IM group, in the SOC of Infections and Infestations (1.6% of ID subjects). In the ID group, the most frequent events in this SOC included nasopharyngitis, bronchitis, and rhinitis (those had a frequency >0.1%).

No unsolicited adverse *reaction* was found to be common either at the PT or at the SOC level in the key elderly studies.

The highest proportion of subjects with moderate or severe unsolicited *reactions* occurred in the SOC of Infections and Infestations in the ID group (0.4%) and the IM group (0.3%). In this SOC, in the ID group, severe reactions included three severe cases of influenza (0.1%), three severe cases of rhinitis (0.1%), two severe cases of bronchitis (0.1%), one severe case of herpes simplex, and one severe case of laryngitis, one severe pharyngitis, one severe respiratory tract infection, and one severe pneumonia. There was no severe injection site reaction.

In the pool of **all studies**, the most frequent unsolicited events and reactions occurred in the same SOCs as in the pool of key studies. Overall frequencies were similar between the ID and the IM group, for each SOC and in terms of relation to vaccination.

In addition to the AEs categorized as common in the pool of key studies, two *AEs* had a frequency >1% in the ID group when all studies are taken into account: headache (1.0%) and injection site pruritus, with a frequency of 1.4% in the ID group, being the only adverse *reaction* categorized as

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common in the pool of all studies in the elderly population. No SOC had a markedly higher frequency in all elderly studies altogether compared to the key studies only.

During the procedure the Applicant has provided new safety data for the 3rd ID vaccination in adults (study GID15) (494 subjects, including 71 for the first time), and for the 2nd vaccination in elderly in GID17 (2 974, including 511 for the first time). Overall the adult safety database has been increased to 3 825 doses of ID Influenza Vaccine 9µg (with the final Micro-Injection System) in 3 049 adults. The elderly database provides safety data after administration of 5 939 doses of ID Influenza Vaccine 15µg in 3 485 elderly subjects.

Results of GID15 (adults) for the third vaccination provided no indication in either the adult or the elderly populations that there is an increase in frequency or severity of adverse reactions following repeated vaccinations, and the ID and IM vaccinations appear to be interchangeable from a safety perspective.

Additional data of a 6-month follow up after a 2nd vaccination in adults and elderly show that the frequency of SAEs and Deaths, including AESI.s, did not increase after revaccination with the ID or the IM route. The Applicant commits to provide remaining data from 2nd and 3rd vaccination in elderly (GID17).

- **Serious adverse events/deaths/other significant events**

GID15
After the second vaccination, 25 subjects (4.7%) in the ID 9µg group had 25 SAEs and 14 subjects (4.0%) had 16 SAEs in the IM 15µg group. In each group, SAEs occurred mostly in the SOC of Injury, Poisoning, and Procedural Complications (mainly fractures) with 6 subjects (1.1%) in the ID group and 5 subjects (1.4%) in the IM group. The next most frequent SOCs in the ID group were Benign, Malignant, and Unspecified Neoplasms (1.1%) and Psychiatric Disorders (0.8%). In the IM group, the next most frequent SOCs were Musculoskeletal and Connective Tissue Disorders in the IM group (0.9%), Nervous System Disorders (0.6%), and Psychiatric Disorders (0.6%).
No deaths occurred.

GID23
Over the whole study a total of 47 subjects experienced 49 SAEsa including three deaths, 39 subjects (2.2%) in the ID 9µg group experienced 41 SAEs and 8 subjects (1.8%) in the IM 15µg group experienced 8 SAEs.

All SAEs were considered to be unrelated to the vaccine or experiment according to both the Investigator and the Sponsor. The time to onset and heterogeneous distribution of these cases across SOCs did not raise any specific area of concern regarding the safety profile of the vaccine.

Three deaths were reported during the 6-month follow-up period, two in the ID 9µg group and one in the IM 15µg. None of these deaths were assessed as related to vaccination according to both the Investigator and the Sponsor.

GID17
VAC1

Overall, in the 6-month period after the first vaccination, 138 subjects (5.3%) in the ID 15µg group and 53 subjects (4.9%) in the IM 15µg group had at least one serious adverse event (SAE). There were no related SAEs in the IM group.

One subject in the ID group had a serious episode of myopericarditis. According to the Investigator, the event could have been related to the study vaccine as it is known that the influenza virus can cause myopericarditis.

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The outcome was fatal for 19 subjects (0.7%) in the ID group and 4 (0.4%) in the IM group, life-threatening for 8 subjects (0.3%) in the ID group and 5 subjects (0.5%) in the IM group.

VAC2
Overall, more than 21 days after the second vaccination, 29 subjects (1.2%) in the ID\ID group, 6 subjects (1.2%) in the IM\ID group, and 6 subjects (1.2%) in the IM\IM group had at least one SAE. No SAEs were considered by the Investigator to be related to the vaccine.

In the ID\ID group, 5 subjects died, 17 recovered, 5 recovered with sequelae, and for 3 subjects the SAE was still ongoing at the end of the follow-up period. In the IM\ID group, 1 subject died and 5 recovered. In the IM\IM group, 1 subject died, 1 recovered, 1 recovered with sequelae, and for 3 subjects the SAE was still ongoing at the end of the follow-up period.

- Laboratory findings

As the ID Influenza Vaccine is manufactured according to a process derived from the Applicant's IM Influenza Vaccine, no clinical laboratory evaluations have been performed during this clinical development program.

- Safety in special populations

Analysis of the influence of gender or risk status on the safety of the Influenza Vaccine revealed similar trends between the ID and the IM group. Overall, there were more vaccinations followed by reactions and events in female than male subjects, and more SAEs were reported in the male population. In Phase III studies, especially in the elderly, the subjects with a risk status had more SAEs in the ID and in the IM groups.

No clinical data on exposed pregnancies are available. A follow-up of pregnancies conducted in GID02, GID15, and GID23 did not reveal any safety signal in the outcome of pregnancies.

- Safety related to drug-drug interactions and other interactions

No drug interaction studies have been performed for the investigational product, although in all studies subjects were not included if vaccination had been performed in the 4 weeks prior to vaccination with the investigational product – or was planned in the 4 weeks following vaccination. This was in order to minimize possible vaccine-vaccine interactions.

- Discontinuation due to adverse events

In the key studies, in both the adult and elderly populations, the proportion of subjects who discontinued due to an AE or SAE was similar between the ID and IM groups within each individual study.

- Post marketing experience

There is no safety data from post-marketing experience with the ID Influenza Vaccine.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the Applicant fulfils the requirements and provides adequate evidence that the Applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

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Risk Management Plan

The MAA submitted a risk management plan

Table Summary of the risk management plan

• Safety Concern	• Proposed Pharmacovigilance Activities (routine and additional)	• Proposed Risk Minimization Activities (routine and additional)
Important Identified Risks: none		
	▪ Not applicable	▪ Not applicable
Important Potential Risks:		
neuritis, encephalomyelitis, Guillain Barre syndrome, convulsion, vasculitis, thrombocytopenia, severe allergic reactions*	▪ Routine Pharmacovigilance activities ▪ The PSURs will provide a cumulative overview on these AESIs and will be delivered during the first two years of post-marketing experience. ▪ A six-monthly evaluation of the incidence of the above potential risks using a large medical record database (THIN) as well as the calculation of reporting rates for other EU countries not included in THIN (a UK only database) will be done. These analyses will examine trends over time and can be provided to EMEA. These analyses will allow for the measurement of the incidence of potential risks or changes in their reporting rates in larger and different populations than those studied during clinical development	Statements in Section 4.8 of the SPC: *Blood and lymphatic system disorders* Transient thrombocytopenia, transient lymphadenopathy *Immune system disorders* Allergic reactions, in rare cases leading to shock, angioedema *Nervous system disorders* Neuralgia, febrile convulsions, neurological disorders, such as encephalomyelitis and Guillain Barré syndrome *Vascular disorders* Vasculitis associated in very rare cases with transient renal involvement *Skin and subcutaneous tissue disorders* Generalised skin reactions including urticaria
Important Missing Information:		
1 - Clinical trials may have identified AEs with a frequency lower 0.04% (about 4 per 10 000). Very rare AEs could not be identified during the clinical development.	▪ Routine Pharmacovigilance activities	▪ Not applicable
2 - Repeated use data in the elderly are not currently available	▪ Topic under investigation in the GID17 clinical trial (2280 subjects); results will be available in 2009.	▪ Not applicable

* This list of Adverse Events of Special Interest (AESI) has been identified for pandemic influenza vaccines by the European Vaccine Manufacturers working group in collaboration with the EMEA considering the annual flu vaccines safety profile as a reference

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

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2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

During the evaluation, two major objections and a number of other concerns related to quality were identified. These have been appropriately addressed by the Applicant and are considered resolved. Two minor unresolved quality issues, having no impact on the Risk-benefit balance of the product, will be resolved as post-approval commitments

Non-clinical pharmacology and toxicology

The safety of the intradermal vaccine was studied in two repeat-dose toxicity studies in rabbits. There was no evidence for systemic toxicity. ID vaccination caused inflammatory reactions at the injection sites at all doses tested, characterized by reversible erythema and edema. Similar observations have been made in the clinic, and the importance of local reactions for the benefit-risk of this product should be based on clinical data.

A developmental toxicity study was conducted in rabbit addressing female fertility, embryo-fetal development (including an evaluation of teratogenicity) and early postnatal development. There were no adverse effects on any of these parameters. Antibodies to the vaccine were observed in both the dams and the foetuses.

Efficacy

The Applicant has provided evidence that the ID route of immunization is at least as immunogenic as the IM route. The immune responses as determined by HI after ID vaccination with 9 µg in the adult population (18-59 years) are non-inferior to the responses to the Applicant's licensed IM influenza vaccine (15 µg/dose) (Vaxigrip). Likewise, the immune responses after ID vaccination with 15 µg/dose in an elderly population (>60 years) were shown to be non-inferior. In addition the immune response in elderly was also shown to be statistically superior to that after IM vaccination with 15 µg/dose. Although the difference between the ID and IM administration routes in elderly was statistically significant, the clinical relevance of the difference is questionable.

Safety

Overall the adult safety database includes 3 825 doses of ID Influenza Vaccine 9µg (with the final Micro-Injection System) administered in 3 049 adults. The elderly database provides safety data after administration of 5 939 doses of ID Influenza Vaccine 15µg in 3 485 elderly subjects. This is considered to be sufficient to describe adverse reactions that occur uncommonly and to give an indication of any rare events.

The ID vaccine is very commonly associated with a range of local and systemic adverse reactions. These adverse events are not often of severe intensity and the safety profile would not preclude the use in adults 18 to 59 years and elderly aged > 60 years.

Although injection site reactions were as expected higher in subjects vaccinated by the ID route than by the IM route, no other data indicate that the safety of this vaccine is different from other authorised IM influenza vaccines.

Medicinal product no longer authorised

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

Based on the justification stated by the MAH regarding the testing of one version only of the PIL, it is acceptable that only the 15 µg strength has been tested.

The legibility test report provided by the applicant is considered acceptable.

Risk-benefit assessment

Context

The active substances present in the vaccine are known and are produced in a manner that is identical to that of the Applicant's IM seasonal Influenza Vaccine, with all excipients present in the ID Influenza Vaccine being also present in the Applicant's IM seasonal Influenza Vaccine. Thus, from the composition point of view it is not anticipated any specific new risk associated with this vaccine.

Benefits

Intanza induces an adequate immune response in adults between 18 to 60 years and in the older than 60 years of age that was general comparable to that induced by a comparator IM vaccine containing 15 µg of antigen.

The vaccine uses a system that delivers the antigens into the dermis. The final Micro-injection system features a pre-filled, ready-to-use syringe with an integral micro-needle that protrudes 1.5 mm from the proximal end of the glass syringe. A benefit of this system compared to the classical intra dermal injection (Mantoux method) is that it overcomes the difficulties associated with the Mantoux method. The short length of the needle minimizes the risk of mechanical damage to nerves and blood vessels during ID administration.

Risk

Intanza is very commonly associated with a range of local and systemic adverse reactions. These adverse events are not often of severe intensity and the safety profile would not preclude the use in adults 18 to 59 years and elderly aged > 60 years.

The current safety database is considered to be sufficient to describe adverse reactions that occur uncommonly and to give an indication of any rare events. All adverse events of special interest will be continuously followed- up and be cumulatively presented in the PSURs as well as be addressed in the RMP.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Balance

The overall B/R of Intanza is positive.

Medicinal product no longer authorised

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Intanza in the following indication:

9 microgram strength:
Prophylaxis of influenza in adults up to 59 years of age, especially in those who run an increased risk of associated complications.

The use of Intanza should be based on official recommendations.

15 microgram strength:
Prophylaxis of influenza in individuals 60 years of age and over, especially in those who run an increased risk of associated complications.

The use of Intanza should be based on official recommendations.

was favourable and therefore recommended the granting of the marketing authorisation.

Medicinal product no longer authorised