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Rapid assessment of the reactogenicity of a 2016-2017 seasonal influenza vaccine: results from a feasibility study

Authors: Anke L. Stuurman[a*], Thomas Verstraeten[a], Antoon De Schryver[b]

[a]P95 Epidemiology and Pharmacovigilance Consulting and Services, Koning Leopold III laan 1, 3001, Leuven, Belgium

[b]IDEWE, Interleuvenlaan 58, B-3001, Leuven, Belgium

*Corresponding author

Anke L. Stuurman: anke.stuurman@p-95.com, +31 6 14502888

Abstract

The European Medicines Agency (EMA) calls for a strategy for enhanced safety surveillance of seasonal influenza vaccines.

Objective: We assessed the feasibility of collecting reactogenicity data within one month of the start of the vaccination campaign in Belgium.

Methods: One hundred subjects aged 18 to 65 years who had received inactivated seasonal influenza vaccine in occupational setting were enrolled. For 7 days after

vaccination, subjects received a daily SMS with a link to a web-based questionnaire where reactogenicity events and their severity were solicited.

Results: Data collection was completed by October 13th, 2016, before the peak of the vaccination campaign in Belgium. 68% of participants reported a local reaction and 65% a general reaction; 51% reported both a local and a general reaction.

Conclusion: Here we show that it has been possible to collect reactogenicity data in adults for enhanced safety surveillance in Belgium in a timely manner. The observed reactogenicity is higher compared to previous observations for this vaccine measured in clinical trials.

Keywords: adults, enhanced safety surveillance, European Medicines Agency guidance, reactogenicity, seasonal influenza vaccine

1. Introduction

In July 2016, the Committee for Medicinal Products for Human Use (CMPH) of the European Medicines Agency (EMA) published a guideline which encompasses regulatory, quality, non-clinical and clinical aspects of influenza vaccines, including seasonal influenza vaccines [1]. To "confirm acceptable tolerability of the newly recommended strains", the CMPH calls for a strategy for enhanced safety surveillance [2]. The aim is to detect a potential increase in reactogenicity and allergic events in near real-time in the earliest vaccinated cohort; in order to mitigate risks associated with potential new safety concerns within the first month after the start of immunisation. This strategy is to be implemented by marketing authorisation holders in one or a few EU Member States, and is to be conducted in addition to basic routine surveillance [2].

In response to this call, we have performed an observational study to assess the feasibility of collecting reactogenicity data rapidly, i.e. within one month, after the start

of the annual influenza vaccination campaign in Belgium. The primary objective was to assess whether reactogenicity data can be collected in a timely manner in Belgium. Secondary objectives were to assess the number of individuals that need to be screened to ensure complete enrolment and the completeness of follow-up among subjects who agreed to participate in the study.

2. Methods

A prospective, non-interventional cohort study was performed among subjects who had received seasonal influenza vaccine through routine clinical practice. EMA guidance calls for at least 100 subjects per age group, in this feasibility study we focused on adults and therefore aimed to enrol 100 subjects aged 18-65 years.

In Belgium, there is no general influenza vaccination recommendation for adults [3], however adults are frequently vaccinated at the workplace. We therefore collaborated with the non-profit organisation IDEWE Occupational Health Services, one of the large groups in Belgium providing services for optimizing health and wellbeing at the workplace, including annual influenza vaccination. Subjects were recruited by IDEWE study nurses during the vaccination campaign at an office of the Flemish government; recruitment ended once 100 subjects were enrolled. Government employees are among the groups first in line to be vaccinated.

Inclusion criteria were age 18 to 65 years, receipt of inactivated influenza vaccine, in possession of a mobile phone (and have it with them at the recruitment site), ability to fill out a web-based questionnaire during 7 days following vaccination and provision of written informed consent. Concomitant administration of another vaccine was an exclusion criterion. Subjects received a daily SMS with a link to the web-based questionnaire. In case of non-response, subjects received one reminder the following

day. Mobile phone number was validated by the study nurse at the time of recruitment. The link to the questionnaire could be opened directly through the SMS on a smartphone, but could also be typed into the browser of e.g. a tablet or laptop. The following adverse events and their severity were solicited in the questionnaire: injection-site pain, erythema, swelling and induration; fever, vomiting/nausea, malaise, headache, decreased appetite, myalgia/arthralgia and allergic reaction [2]. Severity was assessed with previously used grading systems for severity of local and general symptoms [4,5].

We calculated rates with 95% exact binomial confidence intervals for each adverse event individually, for any local adverse event, for any general adverse event, and for both a local and general adverse event.

Ethical approval was obtained from the Committee for Medical Ethics from Antwerp University Hospital. The study has been registered in the EU PAS Register (EUPAS15696).

3. Results

One hundred subjects who met the inclusion criteria were enrolled in the study. The average age of subjects was 41 years (median 41, range 24 to 61 years) and 47% were female.

3.1 Timeliness

The vaccination campaign in Belgium usually takes place between mid-October and mid-November [6]. All subjects were enrolled in the study on October 6th, 2016. The last day of data collection was October 13th, 2016. Therefore, data collection was complete before the peak of the vaccination campaign in Belgium.

3.2 Enrolment rate

In order to enrol 100 subjects, the study nurses actively approached 226 individuals to ask if they were willing to participate in the study, giving an enrolment rate of 44%. The main reasons cited for non-participation were "lack of time" and "did not bring mobile phone". Four individuals who had originally provided informed consent were excluded: three did not bring their mobile phone to the recruitment site and one indicated not to be able to fill out the questionnaire every day.

3.3 Completeness of follow-up

Among 100 enrolled subjects, 78 (78%) completed the questionnaire daily for days 0 (i.e. day of vaccination) through day 6, 85 (85%) completed the questionnaire daily at least for days 0-3, 2 (2%) completed the questionnaire only once and 5 subjects (5%) did not complete any questionnaire. The number of completed questionnaires per day during follow-up was 94, 92, 90, 87, 89, 84 and 86, on days 0-6, respectively.

3.4 Reactogenicity

Reactogenicity data for solicited adverse events are presented in Table 1. All subjects were vaccinated with an inactivated quadrivalent influenza vaccine (Alpharix Tetra ®). 68% of participants reported a local reaction and 65% a general reaction; 51% reported both a local and a general reaction. Injection site reactions typically persisted for 2 days or less.

Table 1. Number and percentage of subjects who reported solicited adverse events in the current study.

When available, comparison data from two clinical trials with earlier formulations of the same vaccine are shown (Table 2). The first is the largest clinical trial with the vaccine,

conducted in multiple centres in Asia, Europe and North America in 2010-2011 in adults aged 18 years and older [7]. The second trial is much smaller but was conducted in Germany, in 2013 in adults aged 18-60 years [8]. The observed reactogenicity is higher compared to previous observations for this vaccine in clinical trials [7,8].

Table 2. Number of subjects who reported solicited adverse events and duration of solicited adverse events in the current study and in two clinical trials with a previous formulation of the same vaccine.

4. Discussion

In this study we have shown that it was feasible to collect reactogenicity data for the adult population aged 18 to 65 years within weeks after the start of the vaccination campaign in Belgium. The enrolment rate was 44% and 78% of the respondents completed the questionnaire every day for the entire duration of follow-up. Eighty-five percent of the respondents completed the questionnaire for at least days 0-3, the time frame within which most mild (local and systemic) reactions resolve [9].

Enrolment rate and rate of completion of follow-up were included to more accurately estimate the amount of time, number of recruitment sites and number of participants required for a full enhanced safety surveillance study. Two study nurses completed enrolment within one day, which was faster than the anticipated 2-3 days.

Only adults aged 18-65 years were included in this feasibility study. In a full study, children 6 months to <18 years and adults >65 years will be included as well. Evidently, it will not be possible to recruit individuals in these age groups from occupational settings, but rather from general practice and hospital settings. Enrolment rates and follow-up times may vary between settings and populations.

As this study was conducted in occupational setting, a healthy worker effect cannot be excluded. The influenza vaccine was offered to all employees at the office, however influenza vaccination is never compulsory in Belgium. Self-selection could lead to more healthy people choosing to accept the vaccine (as part of a healthy lifestyle) or more people with health concerns. However, these effects were not considered to be an issue in this study as they are unlikely to impact reactogenicity. In future years, populations from similar occupational settings where influenza vaccination is offered could be identified, i.a. from government facilities.Observed reactogenicity was higher compared to previous observations for this vaccine measured in clinical trials. This was a non-interventional and unblinded study with no control group, which may have affected the reporting rates. Reactogenicity data from clinical studies might not be fully comparable due to differences in data collection. The relatively high fever rate is likely due to the fact that we relied on self-report of "feeling feverish"; only three respondents measured their temperature, of which one was <38°C. Not measuring temperature when feeling feverish is more likely to yield false-positive reports for fever compared to the more rigorous systematic temperature check that takes place in clinical trials. Furthermore, as participants were reminded to complete the questionnaire on a daily basis, recall bias is expected to be limited; perhaps more so than when using written diary cards without daily reminders, and this may have led to higher reporting rates. The data collected in this study can be used as a baseline to which next year's data can be compared for this age group. Ideally, all influenza vaccine marketing authorization holders would use the same method of data collection in their enhanced safety surveillance strategies as this would simplify comparisons between the available influenza vaccines.

Online data collection has several advantages. Due to the present widespread availability of internet connection (and smartphones), participants can easily complete

the questionnaire at a time and place of their choosing. Additionally, reminders can be sent. Finally, data is available immediately upon last completion of the questionnaire. This is especially important in the context of near-real time enhanced safety surveillance where quick availability of data is of the utmost importance.

Eighty percent of the participants agreed to be contacted again in case additional questions arise. If a new but common adverse event is discovered, we will have access to a pre-recruited group of vaccinated individuals, allowing for an additional round of quick data collection.

5. Conclusion

The strategy of enhanced safety surveillance is part of a broader shift from clinical trials to increased post-licensure monitoring of seasonal influenza vaccines [10]. Rapid data collection is essential for risk mitigation purposes in studies conducted when the vaccine is already in use. In this study we have shown it is feasible to collect reactogenicity data in the adult population aged 18-65 years in Belgium in a timely manner.

Key Issues

- European Medicines Agency calls for a strategy of enhanced safety surveillance of influenza vaccines, to be implemented by marketing authorisation holders.
- The strategy's aim is to detect a potential increase in reactogenicity in near-real time in the earliest vaccinated cohort for risk mitigation purposes.
- Study objective is to assess the feasibility of collecting reactogenicity data rapidly (within 1 month) after the start of the annual influenza vaccination campaign in Belgium.
- This is a non-interventional study among 100 adults (18-65 years) who received influenza vaccine and completed web-based questionnaire on reactogenicity daily for one week.
- We have shown it is feasible to collect reactogenicity data in Belgium in a timely manner.

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Declaration of Interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Reference annotations

** Of interest*

*** Of considerable interest*

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Supplementary material

The questionnaire used in the study is given below. In the web-based version, questions were presented one at the time. As the study took place in Flanders, the original questionnaire was in Dutch (Section A). For your information, an English translation is provided too (Section B). The latter might require fine-tuning of the wording prior to use.

Section A: Original questionnaire

Instructies: Lees de volgende vraag en vink het vakje voor het juiste antwoord aan.

Vandaag is het [datum]. Deze vragen gaan over [datum].

1. Heeft u deze dag pijn gehad rond de injectieplaats?

Ja
Nee

Indien ja:

Hoeveel pijn had u?

De pijn vormde geen belemmering voor mijn activiteiten
De pijn vormde enige belemmering voor mijn activiteiten
De pijn was aanzienlijk en verhinderde mijn dagelijkse activiteiten

2. Heeft u deze dag roodheid van de huid rond de injectieplaats gehad?

Ja
Nee

Indien ja:

Hoe groot was de rode vlek? *Indien mogelijk, gelieve de rode plek met een lineaal op te meten en de grootste diameter op te geven.*

Minder dan 2,5 cm
2,5 tot en met 5,0 cm
5,1 tot en met 10 cm
Meer dan 10 cm

3. Heeft u deze dag zwelling van de huid rond de injectieplaats gehad?

Ja
Nee

Indien ja:

Hoe groot was de zwelling? *Indien mogelijk, gelieve de zwelling met een lineaal op te meten en de grootste diameter op te geven.*

Minder dan 2,5 cm
2,5 tot en met 5,0 cm
5,1 tot en met 10 cm
Meer dan 10 cm

4. Heeft u deze dag verharding rond de injectieplaats gehad?

Ja
Nee

Indien ja:

Hoe groot was de verharding? *Indien mogelijk, gelieve de verharding met een lineaal op te meten en de grootste diameter op te geven.*

Minder dan 2,5 cm
2,5 tot en met 5,0 cm
5,1 tot en met 10 cm
Meer dan 10 cm

5. Heeft u zich deze dag koortsachtig gevoeld?

Ja
Nee

Indien ja:

Heeft u uw temperatuur gemeten?

Ja
Nee

Indien ja:

Wat was de temperatuur?

Lager dan 38.0°C
38.0°C tot en met 38.4°C
38.5°C tot 38.9°C
Hoger dan 39.0 °C

Waar heeft u de temperatuur gemeten?

Oraal (in de mond)
Rectaal (in de anus)
Oksel
Oor

6. Heeft u zich deze dag misselijk gevoeld of heeft u overgegeven?

Ja
Nee

Indien ja:

Hoe ernstig was de misselijkheid en/of het overgeven?

De misselijkheid en/of het overgeven vormde geen belemmering voor mijn activiteiten.
De misselijkheid en/of het overgeven vormde enige belemmering voor mijn activiteiten.
De misselijkheid en/of het overgeven was aanzienlijk en verhinderde mijn dagelijkse activiteiten

7. Heeft u deze dag algehele malaise ervaren (gevoel van slapheid, niet lekker voelen)?

Ja
Nee

Indien ja:

Hoe ernstig was de algehele malaise?

De malaise vormde geen belemmering voor mijn activiteiten.
De malaise vormde enige belemmering voor mijn activiteiten.
De malaise was aanzienlijk en verhinderde mijn dagelijkse activiteiten

8. Heeft u deze dag hoofdpijn gehad?

Ja
Nee

Indien ja:

Hoe erg was de hoofdpijn?

De hoofdpijn vormde geen belemmering voor mijn activiteiten.
De hoofdpijn vormde enige belemmering voor mijn activiteiten.

De hoofdpijn was aanzienlijk en verhinderde mijn dagelijkse activiteiten

9. Heeft u deze dag verminderde eetlust gehad?

Ja
Nee

Indien ja:

Hoe erg was de verminderde eetlust?

De verminderde eetlust vormde geen belemmering voor mijn activiteiten.
De verminderde eetlust vormde enige belemmering voor mijn activiteiten.
De verminderde eetlust was aanzienlijk en verhinderde mijn dagelijkse activiteiten

10. Heeft u deze dag spierpijn of gewrichtspijn?

Ja
Nee

Indien ja:

Hoe erg was de spierpijn en/of gewrichtspijn?

De spierpijn en/of gewrichtspijn vormde geen belemmering voor mijn activiteiten.
De spierpijn en/of gewrichtspijn vormde enige belemmering voor mijn activiteiten.
De spierpijn en/of gewrichtspijn was aanzienlijk en was belemmerend voor mijn dagelijkse activiteiten

11. Heeft u een allergische reactie gehad?

Ja
Nee

Indien ja:

Jeuk zonder uitslag
Plaatselijke jeuk met uitslag (huidverkleuring met bultjes)
Wijdverspreide jeuk met uitslag (huidverkleuring met bultjes) en/of zwelling (vooral in het gezicht)
Anders, namelijk: _____

Section B: Translated questionnaire

Instructions: Read the following question and check the box in front of the correct answer.

Today is the [date]. These questions are about [date].

1. Did you have pain at the injection site on this day?

Yes
No

If yes:

How much pain did you have?

The pain did not interfere with my activities
The pain somewhat interfered with my activities
The pain was considerable and prevented my daily activities

2. Did you have redness of the skin around the injection site on this day?

Yes
No

If yes:

How big was the red spot? *If possible, please measure the red spot with a ruler and report the largest diameter.*

Less than 2,5 cm
2,5 to 5,0 cm
5,1 to 10 cm
More than 10 cm

3. Did you have swelling of the skin around the injection site on this day?

Yes
No

If yes:

How big was the swelling? *If possible, please measure the swelling with a ruler and report the largest diameter.*

Less than 2,5 cm
2,5 to 5,0 cm
5,1 to 10 cm

More than 10 cm

4. Did you have hardening around the injection site on this day?

Yes
No

If yes:

How big was the hardened spot? *If possible, please measure the hardened spot with a ruler and report the largest diameter.*

Less than 2,5 cm
2,5 to 5,0 cm
5,1 to 10 cm
More than 10 cm

5. Did you feel feverish on this day?

Yes
No

If yes:

Did you measure your temperature?

Yes
No

If yes:

What was the temperature?

Below 38.0°C
38.0°C to 38.4°C
38.5°C to 38.9°C
Higher than 39.0 °C

Where did you measure the temperature?

Oral (in the mouth)
Rectum (in the anus)
Armpit
Ear

6. Did you feel nauseous on this day, or did you vomit?

Yes
No

If yes:

How severe was the nausea/vomiting?

The nausea/vomiting did not interfere with my activities
The nausea/vomiting somewhat interfered with my activities
The nausea/vomiting was considerable and prevented my daily activities

7. Did you experience general malaise on this day (feeling of weakness, not feeling well)?

Yes
No

If yes:

Hoe ernstig was de algehele malaise?

The malaise did not interfere with my activities
The malaise somewhat interfered with my activities
The malaise was considerable and prevented my daily activities

8. Did you have a headache on this day?

Yes
No

If yes:

How bad was the headache?

The headache did not interfere with my activities
The headache somewhat interfered with my activities
The headache was considerable and prevented my daily activities

9. Did you have decreased appetite on this day?

Yes
No

If yes:

How bad was the decreased appetite?

The decreased appetite did not interfere with my activities

The decreased appetite somewhat interfered with my activities
The decreased appetite was considerable and prevented my daily activities

10. Did you have muscle aches or joint pains?

Yes
No

If yes:

How bad were/was the muscle aches/joint pain?

The muscle aches/joint pain did not interfere with my activities
The muscle aches/joint pain somewhat interfered with my activities
The muscle aches/joint pain were/was considerable and prevented my daily activities

11. Did you have an allergic reaction?

Yes
No

If yes:

Itch without rash
Local itch with rash (skin discoloration with bumps)
Widespread itch with rash (skin discoloration with bumps) and/or swelling (especially in the face)
Other, please specify: _____

Table 1. Number and percentage of subjects who reported solicited adverse events in the current study.

Solicited AE	Severity	All enrolled subjects (N=100)			Subjects who completed ≥1 questionnaire (N=95)			Subjects who completed all questionnaires (N=78)		
		n	%	[95%CI]	n	%	[95%CI]	n	%	[95%CI]
Injection site AE										
Pain	Any	63	63	[52.8;72.4]	63	66.3	[55.9;75.7]	56	71.8	[60.5;81.4]
	Grade 3[a]	1	1	[0.0;5.4]	1	1.1	[0.0;5.7]	1	1.3	[0.0;6.9]
Erythema	Any	7	7	[2.9;13.9]	7	7.4	[3.0;14.6]	6	7.7	[2.9;16.0]
	Grade 3 (>10cm)	0	0	[0.0;3.6]	0	0.0	[0.0;3.8]	0	0.0	[0.0;4.6]
Swelling	Any	15	15	[8.6;23.5]	15	15.8	[9.1;24.7]	11	14.1	[7.3;23.8]
	Grade 3 (>10cm)	0	0	[0.0;3.6]	0	0.0	[0.0;3.8]	0	0.0	[0.0;4.6]
Induration	Any	34	34	[24.8;44.2]	34	35.8	[26.2;46.3]	28	35.9	[25.3;47.6]
	Grade 3 (>10cm)	0	0	[0.0;3.6]	0	0.0	[0.0;3.8]	0	0.0	[0.0;4.6]
Any of the above injection site AE	Any	68	68	[57.9;77.0]	68	71.6	[61.4;80.4]	59	75.6	[64.6;84.7]
General AE										
Fever	Any[b]	21	21	[13.5;30.3]	21	22.1	[14.2;31.8]	19	24.4	[15.3;35.4]
	Grade 3 (>39°C)	0	0	[0.0;3.6]	0	0.0	[0.0;3.8]	0	0.0	[0.0;4.6]
Vomiting/ nausea	Any	11	11	[5.6;18.8]	11	11.6	[5.9;19.8]	10	12.8	[6.3;22.3]
	Grade 3[a]	1	1	[0.0;5.4]	1	1.1	[0.0;5.7]	1	1.3	[0.0;6.9]
Malaise	Any	31	31	[22.1;41.0]	31	32.6	[23.4;43.0]	29	37.2	[26.5;48.9]
	Grade 3[a]	6	6	[2.2;12.6]	6	6.2	[2.4;13.2]	6	7.7	[2.9;16.0]
Headache	Any	35	35	[25.7;45.2]	35	36.8	[27.2;47.4]	32	41.0	[30.0;52.7]
	Grade 3[a]	3	3	[0.6;8.5]	3	3.2	[0.7;9.0]	3	3.8	[0.8;10.8]
Decreased appetite	Any	13	13	[7.1;21.2]	13	13.7	[7.5;22.3]	13	16.7	[9.2;26.8]
	Grade 3[a]	1	1	[0.0;5.4]	1	1.1	[0.0;5.7]	1	1.3	[0.0;6.9]
Myalgia/ arthralgia	Any	33	33	[23.9;43.1]	33	34.7	[25.3;45.2]	26	33.3	[23.1;44.9]
	Grade 3[a]	2	2	[0.2;7.0]	2	2.1	[0.3;7.4]	2	2.6	[0.3;9.0]
Allergy	Any	2[c]	2[c]	[0.2;7.0]	2[c]	2.1[c]	[0.3;7.4]	2[c]	2.6[c]	[0.3;9.0]
	Grade 3[d]	0	0	[0.0;3.6]	0	0.0	[0.0;3.8]	0	0.0	[0.0;4.6]
Any of the above general AE		65	65	[54.8;74.3]	65	68.4	[58.1;77.6]	56	71.8	[60.5;81.4]
Both										
Injection site AE and general AE	Any	51	51	[40.8;61.1]	51	53.7	[43.2;64.0]	44	56.4	[44.7;67.6]

AE: adverse event

[a] Prevented daily activities.

[b] Reported feeling feverish, 3 measured their temperature (1 oral, 2 axilliary), among which 1 reported temperature <38.0°C only.

[c] One respondents reported local itch with rash; one respondent reported an allergy other than itch, rash or angioedema and categorized "nosebleed and fatigue" as allergy.

[d] Widespread urticaria and/or angioedema.

Table 2. Number of subjects who reported solicited adverse events and duration of solicited adverse events in the present study and in two clinical trials with a previous formulation of the same vaccine

		Current study		**Clinical trial 1 [7]**		**Clinical trial 2 [8]**	
Study characteristics							
Denominator		100		Injection site AE: 3015 General AE: 3011		60	
Year		2016		2010-2011		2013	
Age group (years)		18-65		18+		18-60	
Mean age (years)		41		57.9		38.7	
Female (%)		47		57		53	
Country		Belgium		Multiple		Germany	
Follow-up		Days 0-6		Days 0-6		Injection site AE: days 0-21 General AE: days 0-4	
Solicited AE		**Subjects n(%)**	**Duration in days median; mean**	**Subjects n(%)**	**Duration in days median; mean**	**Subjects, n(%)**	**Duration in days mean**
Injection site AE							
Pain	Any	63 (63.0)	2; 1.9	1096 (36.4)	2.0; 2.1	37 (61.7)	2.2
	Grade 3[a]	1 (1.0)		24 (0.8)		1 (1.7)	
Erythema	Any	7 (7.0)	3; 2.1	58 (1.9)	2.0; 2.4	3 (5.0)	2
	Grade 3 (>10cm)	0 (0.0)		1 (0.0)		0 (0.0)	
Swelling	Any	15 (15.0)	1; 1.6	62 (2.1)	2.0; 2.4	3 (5.0)	2.7
	Grade 3 (>10cm)	0 (0.0)		0 (0.0)		0 (0.0)	
Induration	Any	34 (34.0)	1; 1.6	NA	NA	6 (10.0)	1.8
	Grade 3 (>10cm)	0 (0.0)		NA		0 (0.0)	
General AE							
Fever	Any	21 (21.0)	1; 1.6	48 (1.6)	1.0; 1.8	0 (0.0)	NA

	Grade 3 (>39°C)	0 (0.0)		0 (0.0)		0 (0.0)	
Vomiting/ nausea	Any	11 (11.0)	2; 1.9	NA	NA	NA	NA
	Grade 3[a]	1 (1.0)		NA		NA	
Malaise	Any	31 (31.0)	2; 2.0	NA	NA	NA	NA
	Grade 3[a]	6 (6.0)		NA		NA	
Headache	Any	35 (35.0)	1; 1.6	480 (15.9)	2.0; 2.1	9 (15.0)	1.9
	Grade 3[a]	3 (3.0)		26 (0.9)		1 (1.7)	
Decreased appetite	Any	13 (13.0)	1; 2.0	NA	NA	NA	NA
	Grade 3[a]	1 (1.0)		NA		NA	
Myalgia/ arthralgia	Any	33 (33.0)	1; 2.0	My: 493 (16.4) Ar: 254 (8.4)	My: 2.0; 2.4 Ar: 2.0; 2.8	My: 14 (23.3) Ar: 3 (5.0)	My: 1.8 Ar: 2.7
	Grade 3[a]	2 (2.0)		My: 14 (0.5) Ar: 14 (0.5)		My: 1 (1.7) Ar: 1 (1.7)	
Allergy	Any	2 (2.0)[c]	1; 1.0	NA	NA	NA	NA
	Grade 3[d]	0 (0.0)		NA		NA	

Ar: arthralgia; AE: adverse event; My: myalgia; NA: not available

[a] Prevented daily activities.

[b] Among 21 respondents who reported feeling feverish, 3 measured their temperature (1 oral, 2 axilliary), among which 1 reported temperature <38.0°C only.

[c] One respondents reported local itch with rash; one respondent reported an allergy other than itch, rash or angioedema and categorized “nosebleed and fatigue” as allergy.

[d] Widespread urticarial and/or angioedema.