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Abstract

Oseltamivir or zanamivir are effective in outpatients with seasonal influenza; however, factors associated with response have been incompletely described. During the 2008/2009 epidemic, in a randomized trial for influenza A-infected outpatients, clinical (time to alleviation of flu-related symptoms) and virological (rate of patients with day 2 nasal viral load <200 cgeq/μL) responses to oseltamivir or zanamivir were assessed and associated factors were determined using multivariate analysis. For oseltamivir (141 patients) and zanamivir (149 patients) median times to alleviation of symptoms were 3 and 4 days, respectively; 59% and 34% had virological response. For oseltamivir, a lower clinical response was associated with female gender (HR, 0.53; 95% CI, 0.36–0.79), baseline symptoms score >14 (HR, 0.47; 0.32–0.70), viral load ≥5 log cgeq/μL (HR, 0.63; 0.43–0.93), and initiation of antibiotics (HR, 0.30; 0.12–0.76); a lower virological response was associated with female gender (OR, 0.45; 0.21–0.96), baseline viral load ≥5 log cgeq/μL (OR, 0.40; 0.20–0.84) and days 0–2 incomplete compliance (OR, 0.31; 0.10–0.98). For zanamivir, virological response was associated with age ≥50 years (OR, 0.29; 0.10–0.85) and initiation of antibiotics at baseline (OR, 4.24; 1.07–17.50). Factors associated with lower response to neuraminidase inhibitors in outpatients appeared to be easily identifiable during routine clinical examination and, when appropriate, by nasal sampling at baseline. The unknown association between gender and response to oseltamivir was not explained by compliance.

Keywords: Epidemiological factors, gender, neuraminidase inhibitors, seasonal influenza, treatment outcome
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Introduction

In influenza-infected patients, recent systematic reviews have shown that neuraminidase inhibitors reduce the median time of symptom alleviation in adults and children by approximately 0.5 day [1–3]. Beyond reducing the duration of the disease, antivirals have a variable impact on reducing the viral nasal shedding [4–7].

In 2009 for pandemic A(H1N1) influenza, the World Health Organization recommended the use of neuraminidase inhibitors, oseltamivir or zanamivir, for the treatment of patients with confirmed or strongly suspected influenza infection, when clinical presentation was severe or for patients in higher risk groups [8]. However, factors influencing the clinical and virological responses, which may help

physicians to detect patients who will get the lowest benefit from treatment and have to be particularly followed-up, have been incompletely analysed. Several factors associated with the clinical response in patients receiving oseltamivir were identified in a few studies as: age, high body temperature, delay from onset to treatment start, influenza virus type and infection with an oseltamivir-resistant A(H1N1) virus [9–13]. No specific study has been conducted to evaluate factors influencing the response to zanamivir.

To address these questions, we analysed the data from a double-blind randomized controlled trial performed during seasonal influenza. This trial (Bivir) conducted in France during the A(H3N2) 2008/2009 epidemic, compared the effectiveness of an oseltamivir-zanamivir combination with each of the monotherapies plus placebo. As this trial found an oseltamivir-zanamivir combination to be less effective than oseltamivir monotherapy [14], we chose to analyse data collected only from patients treated with a WHO recommended regimen (i.e. oseltamivir or zanamivir monotherapy). A better understanding of these factors influencing response to neuraminidase inhibitors would provide important insights into the use of antivirals in future seasonal epidemics or pandemics.

Methods

Recruitment and follow-up of participants

The present study is a secondary analysis of data collected in the Bivir trial, a community-based randomized trial, conducted between 7 January and 15 March 2009 (period of the influenza epidemic in France during the winter 2008–2009), reported in detail elsewhere [14]. Briefly, patients were adults over 18 years old who consulted their general practitioner within 36 h of onset of influenza symptoms and had a positive nasal rapid test for influenza A. Exclusion criteria were: vaccination against influenza during the 2008–2009 season; recent exacerbation of COPD; previous history of depression; and known hypersensitivity to neuraminidase inhibitors. Patients gave informed written consent to participate in the study. The protocol was approved by the Ethics Committee of Ile de France 1.

At enrollment (day 0), a nasal swab for virological analysis was performed by the general practitioner before initiation of treatment. In the present study, only day 0 PCR documented influenza A-infected patients, allocated to one of the two oseltamivir or zanamivir monotherapy arms out of three arms of the Bivir trial, were analysed. Oseltamivir (Roche, Bale, Switzerland) dosage was 75 mg orally twice daily; zanamivir dosage was 10 mg by oral inhalation using the commercialized GlaxoSmithKline Diskhaler® (GlaxoSmithKline, Philadelphia, PN, USA), twice daily. The first drug administration was performed in the presence of the general practitioner after the patient had been given instructions on capsule intake and diskhaler use. Treatments were thereafter self-administered twice daily for 5 days. A self-administered questionnaire was given to the patient for self-evaluation of symptoms and notification of drug intake twice daily. A nurse visited the patients on day 2, performed a nasal swab for virological analysis between the 4th and 5th drug intake, and collected data on any adverse event. Patients returned to their general practitioner 2 days (day 7) after completion of treatment for follow-up examination and to report any adverse event. Patients were also contacted by phone on day 14 to collect data on any further adverse events.

Statistical analysis

As in the main analysis of the Bivir trial [14], clinical response was assessed as the time to alleviation of influenza-related symptoms and virological response as the rate of patients with, at day 2, a normalized nasal viral load determined by RT-PCR below 200 cgeq/μL [14].

Factors associated with clinical or virological response were studied separately for oseltamivir and zanamivir by performing univariate and then multivariate analysis, using Cox regression for the clinical response and logistic regression for virological response. The following explanatory variables were studied: gender, age, smoking status, delay from onset of any symptom and start of treatment, baseline symptoms score, baseline fever, baseline physical signs (defined as conjunctival hyperaemia, erythematous throat, congestive eardrum, abnormal chest auscultation, or other), presence at baseline of at least one co-morbidity, or one clinical complication, or initiation of antibiotics, type of influenza virus, baseline normalized viral load, and full compliance between day 0 and day 2 (defined as having perfectly taken up the prescribed treatment during the first 2 days of the trial).

From the univariate analyses results, a multivariate model was built with all variables with p-values <0.10 and then a backward selection approach was used. Then, for each clinical or virological response outcome, a model with all variables remaining in the model either for oseltamivir or for zanamivir, was constructed in order to compare the results of the two drugs with similar adjustments. All analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC, USA).

Results

Clinical and virological responses were assessed, respectively, in the 141 and 149 influenza A-infected outpatients random-

ized to the oseltamivir and zanamivir monotherapy arms. At baseline, for oseltamivir and zanamivir, respectively, mean age was 39.5 and 40.1 years, 52% and 52% were male, and 92% and 87% had H3N2 virus (Table 1). Median times to alleviation of symptoms were 3 days (interquartile range (IQR), 2–7) and 4 days (IQR, 2.5–14), respectively. At day 2, 59% and 34% of patients had a viral load <200 cgeq/μL, and 88% and 85% of the patients had full compliance for days 0–2. A complete description of the patient's characteristics is detailed in the main article of the trial [14].

Clinical response

For oseltamivir, in univariate analysis, explanatory variables with p-values <0.10 were gender, baseline symptoms score >14, baseline normalized viral load ≥5 log cgeq/μL, initiation of antibiotics at baseline, and days 0–2 compliance (Table 2). In the multivariate analysis, a less favourable clinical response was associated with female gender (HR, 0.53; 95% CI, 0.36–0.79), baseline symptoms score >14 (HR, 0.47; 0.32–0.70), baseline normalized viral load ≥5 log cgeq/μL (HR, 0.63; 0.43–0.93), and initiation of antibiotics at baseline (HR, 0.30; 0.12–0.76) (Table 2). Figure 1 presents the time to alleviation of symptoms in the 141 patients treated with oseltamivir according to sex and days 0–2 compliance.

For zanamivir, in univariate analysis, explanatory variables with p-values <0.10 were baseline symptoms score >14 and presence of physical signs (Table 2). In the multivariate analysis, the clinical response was not associated with any explanatory variable (Table 2).

Virological response

For oseltamivir, in univariate analysis, explanatory variables with p-values <0.10 were gender, baseline normalized viral load ≥5 log cgeq/μL and compliance between day 0 and day 2 (Table 3). In the multivariate analysis, a less favourable virological response was associated with female gender (OR, 0.45; 0.21–0.96), baseline normalized viral load ≥5 log cgeq/μL (OR, 0.40; 0.20–0.84) and days 0–2 incomplete compliance (OR, 0.31; 0.10–0.98) (Table 3).

For zanamivir, in univariate analysis, explanatory variables with p-values <0.10 were age ≥50, baseline normalized viral load ≥5 log cgeq/μL, initiation of antibiotics at baseline and days 0–2 compliance (Table 3). In the multivariate analysis, a less favourable virological response was associated with age ≥50 years (OR, 0.29; 0.10–0.85), while a more favourable virological response was associated with an initiation of antibiotics at baseline (OR, 4.24; 1.07–17.50) (Table 3).

Discussion

In the present study, various factors appeared to be associated with the clinical and/or virological responses to neuraminidase inhibitors in the context of the 2008/2009 seasonal influenza, mainly due to H3N2 viruses. Most were clinically relevant data such as: gender, age, baseline score of symptoms, prescription of antibiotics, and compliance. One item of virologically relevant information, nasal viral load at baseline, appears to be independently associated with the response. Different associations of these factors were found depending on the antiviral drug and on whether the clinical or virological response was considered.

Three types of factors were associated with either the clinical or the virological response to oseltamivir: compliance, gender and intensity of the disease, none of these having been previously reported in the literature, possibly because they were not tested. It is a hypothesis that the particular context of a therapeutic trial, with systematic recording of

TABLE 1. Baseline characteristics of the 290 influenza A-infected patients enrolled in the study according to treatment arms

	Oseltamivir, *n* = 141	Zanamivir, *n* = 149
Age (years), mean (SD)	39.5 (13.0)	40.1 (14.1)
[Age range]	[18.1; 76.3]	[18.0; 84.2]
Female, *n* (%)	68 (48.2)	72 (48.3)
Smoker, *n* (%)	15 (10.7)	20 (13.4)
Comorbidities, *n* (%)	20 (14.2)	20 (13.4)
Fever ≥38°C at enrollment, *n* (%)	95 (70.9)	104 (75.9)
Initiation of treatment ≤24 h after onset of symptoms (%)	68 (48.2)	86 (57.7)
Time of initiation of treatment after onset of symptoms (hours), mean (SD)	25.4 (10.7)	24.4 (10.8)
Symptoms score per patient[a],		
mean (SD)	15.3 (3.2)	15.5 (3.1)
% of maximal score[b], mean (SD)	72.7 (15.2)	73.8 (15.0)
Influenza virus subtype, *n* (%)		
H1N1	5 (3.5)	7 (4.7)
H3N2	130 (92.2)	129 (86.6)
Not determined	6 (4.3)	13 (8.7)
Viral load (log cgeq/μL), mean (SD)	4.5 (1.33)	4.3 (1.43)

[a]Sum of the severity of the seven day 0 influenza symptoms (feverishness, nasal stuffiness, sore throat, cough, muscle aches, tiredness-fatigue, and headache) using a four-point scale [5].
[b]The score is expressed as a percentage of the maximal score of 21.

TABLE 2. Association of various factors[a] with less favourable clinical response to oseltamivir or to zanamivir in 290 influenza A-infected patients (univariate and multivariate analysis)

	Oseltamivir (n = 141)					Zanamivir (n = 149)				
	n	Median time to alleviation of flu-related symptoms (IQR)	Univariate analysis		Multivariate analysis	n	Median time to alleviation of flu-related symptoms (IQR)	Univariate analysis		Multivariate analysis
			Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI) p-value			Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI) p-value
Female	68	4.25 (2.50–14.00)	0.57 (0.39–0.83)	0.0036	0.53 (0.36–0.79) 0.002	72	4.00 (2.75–14.00)	0.93 (0.64–1.36)	0.72	0.89 (0.61–1.31) 0.56
Male	73	3.00 (2.00–4.00)				77	4.50 (2.50–14.00)			
Baseline symptoms score >14[b]	90	4.00 (2.50–14.00)	0.50 (0.34–0.74)	0.0004	0.47 (0.32–0.70) 0.0002	99	4.50 (3.00–14.00)	0.70 (0.47–1.05)	0.085	0.72 (0.48–1.08) 0.11
Baseline symptoms score ≤14	49	2.00 (1.00–3.50)				47	3.00 (2.00–7.00)			
Baseline viral load ≥5 log cgeq/μL	61	4.00 (2.00–14.00)	0.70 (0.48–1.02)	0.066	0.63 (0.43–0.93) 0.021	51	7.00 (3.50–14.00)	0.82 (0.55–1.22)	0.33	0.80 (0.53–1.19) 0.27
Baseline viral load <5 log cgeq/μL	80	3.00 (2.00–5.75)				98	4.00 (2.00–14.00)			
Initiation of antibiotics at baseline	11	14.00 (3.00–14.00)	0.40 (0.16–0.97)	0.043	0.30 (0.12–0.76) 0.011	11	2.50 (2.00–7.00)	1.40 (0.71–2.76)	0.34	1.31 (0.65–2.62) 0.45
No initiation of antibiotics at baseline	130	3.00 (2.00–7.00)				138	4.50 (2.50–14.00)			
Physical signs	133	3.00 (2.00–7.00)	1.02 (0.47–2.19)	0.97		141	4.50 (2.50–14.00)	0.45 (0.21–0.99)	0.046	
No physical sign	8	5.75 (1.50–7.00)				8	2.75 (2.00–3.00)			
Days 0–2 incomplete compliance	17	7.00 (1.50–14.00)	0.56 (0.29–1.08)	0.086		22	7.00 (2.00–14.00)	0.75 (0.42–1.31)	0.30	
Days 0–2 full compliance	124	3.00 (2.00–7.00)				127	4.00 (2.50–14.00)			

[a]Other explanatory variables (including age, smoking status, delay from onset of any symptoms and start of treatment, baseline fever, presence of at least one co-morbidity, presence of at least one clinical complication at baseline, type of influenza virus) were not significantly associated with oseltamivir or zanamivir clinical response in univariate analysis (p-values < 0.10).
[b]Symptom score calculated, respectively, for 139 and 146 patients in oseltamivir and zanamivir arms.

FIG. 1. Proportion of the 141 influenza A-infected patients with alleviation of symptoms when treated with oseltamivir plus placebo according to sex (female dark lines, male grey lines) and days 0–2 compliance (full compliance continuous lines, incomplete compliance dotted lines). Alleviation of symptoms defined by the presence of no symptoms of nasal stuffiness, sore throat, cough, muscle aches, tiredness-fatigue, feverishness, and headache or only mild ones, for at least 24 h.

detailed clinical and virological data, may have favoured their detection. The lower response in less compliant patients is expected, as previously reported in chronic diseases [15–17], although less frequently assessed in acute situations of infection. It confirms, if necessary, the clear efficiency of oseltamivir. In contrast, the less favourable both clinical and virological responses in women are not usually described. In contrast to what has been suggested in some other studies [18,19], the effect of gender in the present study was not found to be associated with compliance (no interaction with compliance in the model and no significant difference between men and women for compliance, data not shown) (Fig. 1). Similar results were obtained in another study, which found that male gender and low adherence to treatment were negatively and independently associated with hypertension control [20]. The role of endocrinological characteristics has been advocated to influence the immune response [21,22]; it cannot be here investigated due to the lack of such information available in the database of the trial. The fact that gender was not associated with the response to zanamivir may suggest that its impact on the response to oseltamivir is specific to some pharmacological characteristics that differ between the two drugs. Indeed, unlike zanamivir, which is delivered as the active compound, oseltamivir is delivered as an inactive prodrug. After oral administration, oseltamivir is readily absorbed from the gastrointestinal tract and extensively converted in the liver to the active metabolite, oseltamivir carboxylate, by an esterase [23]. One

TABLE 3. Association of various factors[a] with less favourable virological response to oseltamivir or to zanamivir in 290 influenza A-infected patients (univariate and multivariate analysis)

	Oseltamivir (n = 141)					Zanamivir (n = 149)				
			Univariate analysis		Multivariate analysis			Univariate analysis		Multivariate analysis
	n	Nasal viral load <200 cgeq/μL n (%)	odds ratio (95% CI)	p-value	odds ratio (95% CI)	p-value	n	Nasal viral load <200 cgeq/μL n (%)	odds ratio (95% CI)	p-value	odds ratio (95% CI)	p-value
Female	68	34 (50.00)	0.49 (0.25–0.97)	0.040	0.45 (0.21–0.96)	0.040	72	26 (36.11)	1.25 (0.63–2.47)	0.52	1.18 (0.56–2.46)	0.66
Male	73	49 (67.12)					77	24 (31.17)				
Age ≥50[b]	35	21 (60.00)	1.06 (0.49–2.32)	0.88	1.58 (0.64–3.92)	0.32	36	5 (13.89)	0.25 (0.09–0.70)	0.0075	0.29 (0.10–0.85)	0.023
Age <50	106	62 (58.49)					112	44 (39.29)				
Baseline viral load ≥5 log cgeq/μL	61	29 (47.54)	0.44 (0.22–0.87)	0.018	0.40 (0.20–0.84)	0.015	51	11 (21.57)	0.42 (0.19–0.91)	0.028	0.44 (0.19–1.01)	0.052
Baseline viral load <5 log cgeq/μL	80	54 (67.50)					98	39 (39.80)				
Initiation of antibiotics at baseline	11	4 (36.36)	0.37 (0.10–1.32)	0.13	0.27 (0.06–1.14)	0.074	11	7 (63.64)	3.87 (1.08–13.91)	0.038	4.24 (1.07–17.50)	0.040
No initiation of antibiotics at baseline	130	79 (60.77)					138	43 (31.16)				
Days 0–2 incomplete compliance	17	5 (29.41)	0.25 (0.08–0.74)	0.013	0.31 (0.10–0.98)	0.046	22	3 (13.64)	0.27 (0.08–0.96)	0.043	0.310 (0.08–1.20)	0.091
Days 0–2 full compliance	124	78 (62.90)					127	47 (37.01)				

[a]Other explanatory variables (including smoking status, delay from onset of any symptoms to start of treatment, baseline symptoms score, baseline fever, baseline physical signs, presence of at least one co-morbidity, presence of at least one clinical complication at baseline, type of influenza virus) were not significantly associated with oseltamivir or zanamivir virological response in univariate analysis (p-values < 0.10).
[b]Age calculated for 148 patients in zanamivir arms.

hypothesis could thus be a gender difference during the hepatic process of oseltamivir transformation into the active compound, which seems to be more active in men compared with women, as suggested in one previous publication [24]. In an animal model, with another drug, indinavir, such an influence of the differential status of an enzyme involved in the metabolism of the drug has been described between men and women [25]. Another hypothesis for the lower clinical response to oseltamivir might be that women would declare a higher intensity of symptoms in the course of the disease [26]. However, such a hypothesis would not explain the influence of gender on the virological component of the response. Whether the severity of the symptom at baseline was different in men and women was assessed in the study and found not to be different (data not shown). If this association is confirmed by other studies, it might lead to the proposition that dosage of oseltamivir should be adjusted in women, to achieve similar efficacy as in men. This could prove of importance in patients with complicated or severe influenza, including when i.v. administration is needed. This study also found that the more severe the disease, as suggested by symptom score and viral load at baseline, the lower the clinical and virological responses in patients treated with oseltamivir. This corroborates previous results showing that higher fever was associated with a lower response rate [9,27]. Even if it seems logical, this had not been clearly demonstrated for virological determinants, maybe also because quantitative assessment of viral load by real-time RT-PCR has been introduced only recently and has not been used extensively in such a trial design.

It is noteworthy that a limited number of studies have assessed specifically which factors were associated with the response to zanamivir. In the present study, no variables were found to influence significantly the clinical response to zanamivir. The only factor associated with a poor virological response to zanamivir was older age. The effect of age has already been reported for clinical response to oseltamivir in two previous studies, but not for zanamivir. In one study, oseltamivir appeared clinically less effective in young children, between 0 and 6 years, compared with patients aged 16–64 years [28]. In the other study, which included children between 1 and 12 years, a similar effect was observed [27]. Because patients younger than 18 were not included in the Bivir trial, this association with younger age cannot be assessed in our study. Whether older people in the Bivir trial would have had more difficulties in using the Diskhaler device required for delivery of zanamivir remains a question.

Initiation of antibiotics at baseline was the only factor for which the association was in the opposite direction for oseltamivir and zanamivir. Such a factor has not been studied in

previous publications, and the limited number of patients given antibiotics in our study makes interpretation of these data hazardous. One could suggest that for oseltamivir response it might be considered as a proxy for the intensity of the disease at baseline, as were symptom scores and viral load. It is less easy to explain the positive effect of antibiotics at baseline on the response to zanamivir. It may be more directly related to the antibacterial effect; a hypothesis would be that, in reducing the possible bacterial co-infection, antibiotic treatment would allow more efficient local diffusion and action of the antiviral drug.

We must recognize several limitations to this study. The presence of a control placebo group might have been helpful to distinguish factors associated with the natural history of the influenza infection and those truly linked to the response to antiviral treatment. This choice of a no placebo-placebo group in the Bivir trial was based on the following reasons: (i) it is proved that neuraminidase inhibitors reduce the median time of symptom alleviation in adults and children by approximately 0.5 days, and have a variable impact on reducing the viral nasal shedding; and (ii) neuraminidase inhibitors are recommended in France to treat patients with risk factors. Another limitation is the sample size of our study, which was relatively small, and could be responsible for a lack of detection of some associations. The present study was a secondary analysis of data collected in a community-based randomized trial, and the number of patients included corresponds to the number of patients included in the oseltamivir or zanamivir arms of the Bivir therapeutic trial. The counterpart is that it allowed a parallel assessment of the same factors, which were recorded prospectively for the two drugs in exactly similar conditions. It could explain why some factors already known as influencing the response of oseltamivir have not been found in our study. For instance 'Time from the onset of any symptoms to the start of treatment', demonstrated in several studies [9,29,30], has been tested as variable factor in our study, but was not associated with the response for oseltamivir or zanamivir. The limitation is that subjects in the Bivir trial were adults older than 18 years who consulted their general practitioner and were included quickly after the onset of the disease, within 36 h of influenza symptoms onset.

Factors associated with a lower response to oseltamivir or zanamivir appeared to be easily identifiable during routine clinical examination and, when appropriate, by nasal sampling at baseline. The association between gender and response to oseltamivir, unknown until now, was not linked to the effect of compliance. If it is confirmed, other hypotheses remain to be investigated.

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Conflict of Interest

Thierry Blanchon has received funds for travel for a scientific conference from Roche, is a member of the scientific committee of the GEIG. France Mentré has received funds from Roche, preclinical pharmacokinetic department, for a course on MONOLIX in December 2008. Anne Mosnier has membership of the ministry of health advisory board on influenza, involvement in some epidemiological studies partially or fully funded by Roche and GSK, has received funds for travel for participation in scientific meetings from Roche, and is a member of the scientific committee of the GEIG. Fabrice Carrat is a member of the ministry of health advisory board on influenza and the national public health council, and participated in scientific boards for Novartis and GSK. Xavier Duval has received funds for travel for a scientific conference from GSK and Roche, and lecture fees from Roche and Gilead. Vincent Enouf has membership of the ministry of health advisory board on influenza and has received lecture fees from DANONE. Catherine Leport is associated expert to the national public health council. The other authors have no conflict of interest to declare.

Author Contribution

Designed the experiments/the study: TB, FM, CCO, QD, AM, MB, FC, XD, VE, CL. Analyzed the data: TB, FM, QD, XD, VE, CL. Collected data/did experiments for the study: TB, FM, CCO, AM, MB, XD, VE, CL. Wrote the first draft of the paper: TB, FM, QD, XD, VE, CL. Contributed to the writing of the paper: TB, FM, CCO, QD, AM, MB, FC, XD, VE, CL. Obtained funding: FM CL.

Transparency Declaration

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che clinique, AOM 06060 and AOM 08209). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Appendix

Bivir Study Group membership

Scientific committee (trial design, trial conduct and data interpretation): Steering committee: Leport C (principal investigator), Andreoletti L, Blanchon T, Carrat F, Duval X, Guimfack A, Lina B, Loubière S, Mentré F, Mosnier A, Tibi A, Tubach F, van der Werf S. Clinical study manager: Charlois-Ou C. Other members: Bouscambert-Duchamp M, Bricaire F, Cohen JM, Enouf V, Flahault A, Moatti JP, Vincent C, Vogel JY.

Invited members (informed of study design but did not participate in any decision-making study discussions; supplied drugs and placebos): Eid Z (GSK), Peurichard C (GSK), Pecking M (Roche), Dantin S (Roche), Gysembergh-Houal A (AP-HP).

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