CLINICAL STUDY REPORT: SUMMARY OF RESULTS

V 1.0 01 AUGUST 2024

GOSCI Study

Efficacy of Oscillococcinum® in the treatment of Influenza-like-illness symptoms: a multicentre, randomised, controlled trial in France and Belgium

Study Number:	BRN-C-2019-02
Study Phase:	4
Study code:	GOSCI
EudraCT Number:	2020-002972-11
Compound:	Oscillococcinum ®
Indication	Influenza-like-illness symptoms:
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First patient enrolled	05 NOV 2020

Title

Efficacy of Oscillococcinum® in the treatment of Influenza-like-illness symptoms: a multicentre, randomised, controlled trial in France and Belgium – the GOSCI study

Background

Influenza-like illness (ILI) is a diagnosis of possible influenza or other illness resulting in a common set of clinical symptoms (1-5). The Official Journal of the European Union (OJEU) defines ILI as a sudden onset of symptoms including at least one of the three following respiratory symptoms: cough, sore throat, shortness of breath and at least one of the four following general systemic symptoms: fever or feverishness, headache, malaise, myalgia (1). In uncomplicated ILI, quick alleviation of the symptoms is often the primary goal of the therapy. Self-medication plays an important role. The most often recommended therapies are antipyretics (half of the cases), oral or nasal sprays, combined treatments and homeopathy for a quarter of cases (6,7).

Oscillococcinum® is a homoeopathic preparation of a specific extract from Anas barbarie liver and heart. Oscillococcinum® is traditionally used in the relief of flu-like symptoms such as fever, headache, chills, and body aches. The efficacy of Oscillococcinum® in the prevention and treatment of ILI was evaluated in several clinical studies more than 20 years ago through. In particular, two phase III studies demonstrated a potential significant effect on Oscillococcinum® on ILI. The study conducted by Ferley et al. (1989), among 478 patients (241 placebo / 237 Oscillococcinum®) showed that 17% of patients among the Oscillococcinum® group recovered from ILI symptoms at 48h, compared to 10.3% in the placebo group (p=0.03) (8). Another controlled and randomised study, conducted by Papp et al. (1998) among 372 patients (184 placebo / 188 Oscillococcinum®) demonstrated that the proportion of patients with no symptoms was significantly higher in the verum group from the second day onwards (verum: 17.4%, placebo: 6.6%) until the end of the patients' recording on day 5 in the evening (verum: 73.7%, placebo: 67.7%) (9).

In this context and as Oscillococcinum® is still used in many countries, the present study was designed to provide updated data on the benefit of its use for the treatment of ILI.

Methods

Objectives

The primary objective was:

- To evaluate the efficacy of Oscillococcinum® in the alleviation of ILI symptoms within 72h following the beginning of the first intake of medication

The secondary objectives were:

- To assess the effects of Oscillococcinum® on 1/the alleviation of ILI symptoms within 72h and maintained over at least 24h, 2/the alleviation of ILI symptoms within 48h following the beginning of treatment, 3/the reduction of time to alleviation of symptoms, 4/the improvement of the ability to perform daily activities;
- To describe the effects of Oscillococcinum® on 1/the improvement of sleep quality, 2/the alleviation of other symptoms (fatigue, nasal congestion and gastro-intestinal disturbances), 3/the development of secondary complications;
- To describe the patient's compliance regarding the use of Oscillococcinum®;
- To evaluate the tolerability of Oscillococcinum®;
- To evaluate the patients' and physicians' satisfaction regarding the efficacy of Oscillococcinum®.

Design

The GOSCI study was a prospective, randomised, double-blind, placebo-controlled, multicenter study in France and in Belgium with two parallel groups. Patients were enrolled in the study when they had ILI symptoms confirmed by investigators for less than 12h ideally, and up to 24h maximum at the time of the study treatment start. Investigators of the study were general practitioners (GPs) regardless of their homeopathic prescribing habits. Patients were randomised at a rate of 1:1 to receive either Oscillococcinum® or placebo. Randomisation was stratified according to patient's severity at baseline (mild/moderate/severe) and Influenza vaccination during the winter season or not.

The study comprised a treatment period of 3 days and a follow-up period of 7 days. Patients were required to record their ILI symptoms and fever in an electronic/paper diary three times per day for the 72h following the first treatment dose, then twice a day until the final visit at Day 10.

Inclusion Criteria

- Aged ≥ 18;
- Patients accepting to participate in the study through signing informed consent;
- Patients with ILI defined as sudden onset of symptoms and at least one of the following systemic symptoms: fever (≥37.8°C) or feverishness (feeling of fever or a chill), malaise, headache, myalgia (= assessment mild, moderate or severe for at least one of these symptoms) and at least one of the following respiratory symptoms: cough, sore throat, shortness of breath (= assessment mild, moderate or severe for at least one of these symptoms), less than 24 hours duration;
- Patients able to take the first dose of study medication in the 24 hours following the first symptoms of ILI;
- Patients agreeing to receive notifications by SMS and/or email to remind them of the diary completion.

Exclusion Criteria

- Patients refusing to sign the informed consent;
- Patients with unstable and uncontrolled renal, cardiac, pulmonary, vascular, neurologic, metabolic (diabetes, thyroid disorders, adrenal disease), or immunodeficiency disorders, cancer, hepatitis, cirrhosis, asthma or chronic obstructive pulmonary disease (COPD);
- Participation in a clinical study with an investigational drug within 4 weeks prior to study entry;
- Patients who experienced a previous episode of acute upper respiratory tract infection (URTI), sinusitis, bronchitis, otitis or pneumonia within 4 weeks prior to the Initial Visit;
- Patients taking corticosteroids or immuno-suppressant therapies within 2 months prior to the Initial Visit;
- Patients with evidence/history of alcoholism, drug abuse, psychiatric disorders (including dementia or dementia like syndrome) or any other medical condition that could affect data collection;
- Treatment within 2 weeks prior to the Initial Visit with antiviral drugs such as neuraminidase inhibitors (Tamiflu®, Relenza®, Inavir®), or amantadine (Symmetrel®);
- Treatment within 1 week prior to Initial Visit with Oscillococcinum® or antibiotics related to respiratory tract infection;
- Treatment within 1 week prior to Initial Visit with antipyretics other than paracetamol, analgesics, decongestants;

- Treatment within 1 week prior to Initial Visit with homeopathic medicine related to ILI at baseline or any other herbal medicine product or dietary supplement known to affect immune and/or inflammatory response;
- Patients with any other disease that requires immediate start of antibiotic treatment related to respiratory tract;
- Pregnant or breast-feeding women;
- Patients with intolerance of fructose, malabsorption of glucose or galactose, sucrase/isomaltase deficit;
- Any other condition which according to the investigator's judgement is not compatible with the principles of the study, e.g. inability to give informed consent, inability to complete the electronic diary;
- (For France) Unaffiliated or non-beneficiary of a social security system patient as well as deprived of liberty (article L1121-6 of Code de la Santé Publique) or protected (article L1121-8) adults. (For Belgium) Adult patient deprived of liberty or incapable.

Treatment

Investigational product

Oscillococcinum® and placebo as doses of globuli with one dose containing 1 g of globuli were the administered study medications. The dosage forms, dosage strengths, and batch numbers are summarised Table S1. Oscillococcinum® and placebo were taken 3 doses per day over 3 days. Each dose was taken orally. Patients were instructed to take all 9 doses as scheduled even if they were free of symptoms. The investigational drug blind was maintained using the IWRS.

Table S1: Identity of the investigational product

	Experimental	Control
Product:	Oscillococcinum®	Placebo
Composition:	1 g of globuli composed of : the extract from Anas barbariae, hepatis and cordis 200K 0.85 g sucrose 0.15 g lactose.	1 g of globuli composed of : 0.85 g sucrose 0.15 g lactose.
Dose:	one dose 3 times daily for 3 days	one dose 3 times daily for 3 days
Administration route:	Oral	Oral
Dosage form:	Pilules in single-dose container	Pilules in single-dose container
Manufacturing company:	Laboratoire Boiron	Laboratoire Boiron

Rescue medication

Patients were advised by investigators to take paracetamol only when fever and/or pain could not be tolerated or if the discomfort was too high. Patients were asked to avoid paracetamol intake within 4 hours prior to completion of the diary in the morning, at noon and in the evening, if possible.

Concomitant treatment

All concomitant therapy had to be documented in the diary. The following medications were not recommended from the Initial Visit to the Final Visit: 1/ analgesics / antipyretics except paracetamol;, 2/ decongestants, antibiotics, antiviral treatment against influenza ; 3/ herbal products against influenza, common cold or infections of the upper respiratory tract: ambroxol, bromhexine and

codeine ; 4/ any herbal medicine or dietary supplement known to affect immune and inflammatory response (Extracts from Echinacea, Fabaceae, ….); 5 / acetylcysteine, vitamin C, dextromethorphan ; 6/ immunosuppressives, cytostatic drugs, glucocorticosteroids. However, the patient had the possibility to indicate any uptake of one or several of the above treatments in the diary.

Efficacy Endpoints

The primary endpoint

The primary endpoint was the alleviation of symptoms within 72 hours. It was defined as the alleviation of all symptoms (which were present at baseline) 72h after the first intake of study medication. Alleviation corresponded to the decrease of at least one stage of severity for each symptom recorded at inclusion. ILI symptoms comprised three respiratory symptoms (cough, sore throat, shortness of breath) and four systemic symptoms (fever ([body temperature ≥ 37.8°C] or chills, headache, myalgia, malaise). The diary documentation was used for the estimation.

The secondary efficacy endpoints:

- Alleviation of ILI symptoms within 72h and maintained over at least 24h;
- Alleviation of symptoms within 48 hours;
- Time to alleviation of symptoms of ILI;
- Effect on daily activities;
- Effect on sleep quality;
- Effect on alleviation of other symptoms withing 72h (including fatigue, nasal congestion and gastro-intestinal disturbances);
- Effect on secondary complication;
- Patients' compliance;
- Patients 'satisfaction.

Safety Endpoints

The following endpoints were described (MedDRA version v23.0 was used for coding):

- Total number of AE, SAE;
- Numbers and proportions of patients with at least one AE or SAE by subject;
- Incidence of all AEs, regardless causality to study treatment, by System Organ Class (SOC) and Preferred Terms (PT);
- Incidence of all AEs, related to study treatment, by SOC and PT terms;
- Incidence of SAEs regardless causality to study treatment, by SOC and PT terms;
- Incidence of SAEs related to study treatment, by SOC and PT terms;
- Proportion of patients with at least one AE/SAE leading to permanent discontinuation of study treatment;

Sample Size

The primary endpoint of this study was to compare the proportion of patients with alleviation of ILI symptoms at 72h following the treatment start, in the Oscillococcinum® and placebo groups and to demonstrate the superiority of Oscillococcinum® compared to placebo on the defined endpoints. In the Papp study (9), the difference between the two groups regarding 'clear improvement' of the symptoms reached 10% and the difference regarding 'improvement' reached 5%. Assuming a proportion between these two estimations reaching 7% (i.e. 33% in the placebo group as in the Papp

study - vs 40% in the Oscillococcinum® group), with a power of 80% and a unilateral test with an alpha-risk at 5%, a number of 287 patients in the two groups was estimated, thus 574 globally. Accounting for approximately 10% of non-analysable patients at 72h, around 640 patients were expected to be included in the study (320 in each treatment group).

Statistical Methods

The statistical methodology is detailed in the Statistical Analysis Plan v1.0 validated on August 7th, 2023. Statistical analysis was carried out using SAS software (version 9.4, SAS Institute, North Carolina, USA). Main populations were:

- **Randomised population**: all patients enrolled (randomized) in the study
- **Safety analysis set**: all patients who received at least one dose of study medication. It included any patient who accidently received study medication even not randomised in this study.
- **Full analysis set (FAS):** defined according to the intention-to-treat principle, to consider all randomised patients who received at least one dose of study medication.
- **Per-Protocol (PP) analysis set**: a subset of the full analysis set excluding patients with major protocol deviations.

For comparative analyses (except primary analysis), statistical tests were one-sided and the alpha risk was 5%. In comparison of independent groups (e.g. study treatment vs placebo) two means of quantitative variables were compared using the Student's T test if the normal distribution (Shapiro-Wilk test) and the assumption of homogeneity of variance was verified (the Satterthwaite method was used if the variances were unequal). If the assumptions were not verified, Stratified Wilcoxon (Van Elteren). The comparison of a categorical variable between two independent groups were assessed with the Pearson's Chi-square test. Groups of categories were proposed or the Fisher's exact test was performed when the theoretical number was less than 5. Cochran Mantel-Haenszel test was also used to take into account the stratification factors.

A relative risk ratio (RR) compared the risk of a health event (alleviation of ILI symptoms) among one group with the risk among another group. The two groups were differentiated by demographic factors as gender or exposure to a suspected risk factor.

A multivariate analysis was conducted to assess and compare the efficacy, i.e. the proportion of patients with alleviation of ILI symptoms within 72h between the treatment groups (=forced variable), adjusted for other variables. A stepwise multivariate logistic model was performed, and outcomes were expressed as odds ratios with 95% CI and p-values.

For each subgroup of interest, the relationship with each concerned primary or secondary endpoint (efficacy on the alleviation of ILI symptoms) was tested using a multivariate logistic model. Odd ratios (with 95% CI associated) were presented with significance level p-value. In each model, the subgroup was included, adjusted for treatment arm. The analysis of sleep quality data (after the first treatment dose) over time between treatments arms was performed as a repeated-measures analysis using all available timepoints. The analysis used mixed analysis of variance (ANOVA) model. Survival analysis were used to analyse time-to-event endpoints (such as time to alleviation of ILI symptoms).

Results

Disposition of Patients

Of the 50 opened sites (see the list at the end of the summary), 30 (27 in France and 3 in Belgium) were active recruiting sites and enrolled 683 patients. Patient enrolment occurred in France from November 2020 through April 2023 for 30 months and in Belgium from November 2021 through December 2022 for 14 months.

Of the 683 recruited patients, 680 patients were randomised to receive Oscillococcinum® (Ocs) (n=342) or placebo (Pbo) (n=338) and constituted the safety and FAS populations from which 3 patients were excluded due to non-conformity with the informed consent. Of the 680 FAS patients, 545 (80.1%) (268 in the Oscillococcinum® group and 277 in the placebo group), 525 (77.2%) (266 in the Oscillococcinum® group and 259 in the placebo group) and 504 (74.1%) (252 in the Oscillococcinum® group and 252 in the placebo group) patients completed the diary at 48, 72 and 96 hours, respectively. The PP analysis set included 664 patients, 333 and 331 patients in the Oscillococcinum® and placebo groups, respectively, with 19 patients excluded from the PP population.

Demographic Baseline Characteristics – FAS Population

Demographic characteristics at baseline:

Demographic characteristics at baseline are detailed in Table S2. The median age was 36.5 years (IQR 27;48) in the Oscillococcinum® group and 36.5 years (IQR 27;50) in the placebo group. The FAS population included 506 female patients (74.4%) of whom 259 (75.7%) were in the Oscillococcinum® group and 247 (73.1%) in the placebo group. Of them, 21.8% of patients had comorbidities at baseline (Oscillococcinum® group: 23.7%, placebo group: 19.8%). Of the reported comorbidities, the most frequent were high blood pressure (31.1%), asthma (16.9%), diabetes (10.1%), high cholesterol (8.8%), depression (8.1%) and other disease (48.6%). In total, 16.1% of patients (Oscillococcinum® group: 15.2%, placebo group: 16.9%) had at least one infection during the three years prior to the study, mostly respiratory infections. Few patients reported alcohol consumption (Oscillococcinum® group: 4.1%, placebo group: 5.3%) or tobacco use (Oscillococcinum® group: 12.9%, placebo group: 16.6%). Around a quarter of patients (Oscillococcinum® group: 23.1%, placebo group: 26.4%) practised physical activity.

Table S2: Demographic characteristics at baseline (FAS, N=680)

			Osc (N=342)	Placebo (N=338)	Total - FAS (N=680)
Gender	Male		83 (24.3%)	91 (26.9%)	174 (25.6%)
	Female		259 (75.7%)	247 (73.1%)	506 (74.4%)
Age at diagnosis* (years)	Missing		0	0	0
	Analysed number		342	338	680
	Mean (±SD)		39.5 (± 15)	38.9 (± 14)	39.3 (± 14.5)
	Median		36.5	36.5	36.5
	Q1-Q3		27 - 48	27 - 50	27 - 49
	Min-Max		18 - 86	18 - 74	18 - 86
Age at diagnosis (classes)	<30 years		107 (31.3%)	107 (31.7%)	214 (31.5%)
	≥30 years		235 (68.7%)	231 (68.3%)	466 (68.5%)
At least one comorbidity		Yes	81 (23.7%)	67 (19.8%)	148 (21.8%)
		No	261 (76.3%)	271 (80.2%)	532 (78.2%)

		Osc (N=342)	Placebo (N=338)	Total - FAS (N=680)
If yes, number	1	57 (70.4%)	47 (70.1%)	104 (70.3%)
	2	18 (22.2%)	9 (13.4%)	27 (18.2%)
	3	4 (4.9%)	7 (10.4%)	11 (7.4%)
	≥4	2 (2.4%)	4 (6.0%)	6 (4.1%)
High blood pressure		26 (32.1%)	20 (29.9%)	46 (31.1%)
Heart failure		1 (1.2%)	0 (0.0%)	1 (0.7%)
Arrhythmia		1 (1.2%)	0 (0.0%)	1 (0.7%)
Cerebrovascular accident		1 (1.2%)	3 (4.5%)	4 (2.7%)
Myocardial infarction		0 (0.0%)	0 (0.0%)	0 (0.0%)
Recent surgery		0 (0.0%)	0 (0.0%)	0 (0.0%)
High cholesterol		8 (9.9%)	5 (7.5%)	13 (8.8%)
Chronic obstructive pulmonary disease (COPD)		0 (0.0%)	2 (3.0%)	2 (1.4%)
Asthma		13 (16.0%)	12 (17.9%)	25 (16.9%)
Depression		6 (7.4%)	6 (9.0%)	12 (8.1%)
Anxiety		1 (1.2%)	3 (4.5%)	4 (2.7%)
Diabetes		6 (7.4%)	9 (13.4%)	15 (10.1%)
Kidney disorders		0 (0.0%)	0 (0.0%)	0 (0.0%)
Liver disorders		0 (0.0%)	0 (0.0%)	0 (0.0%)
Obesity		3 (3.7%)	5 (7.5%)	8 (5.4%)
Auto-immune disease		4 (4.9%)	2 (3.0%)	6 (4.1%)
Cancer		0 (0.0%)	1 (1.5%)	1 (0.7%)
At least one other disease		39 (48.1%)	33 (49.3%)	72 (48.6%)
BMI (kg/m²)	Missing	1[&]	0	1[&]
	Analysed number	341	338	679
	Mean (±SD)	25.1 (± 5.1)	25.6 (± 5.8)	25.4 (± 5.5)
	Median	24	24.5	24.4
	Q1-Q3	21.6 - 27.7	21.8 - 28	21.7 - 27.8
	Min-Max	16.7 - 46.4	14.1 - 48.4	14.1 - 48.4

* Age (years) = Year (initial visit date) – Year(birth date) ; BMI (kg/m²) = Weight (kg) / Height² (m). [&] The weight, height, and BMI data for one subject are not used for this table (Height= 1.16 m, Weight=90 kg and BMI= 66.88 kg/m²).

Prior therapies:

A total of 74 patients (10.9%), 11.1% in the Oscillococcinum® group and 10.7% in the placebo group, had received the seasonal influenza vaccination while 77.1% had been vaccinated against SARS-CoV2 (78.5% in the Oscillococcinum® group and 75.8% in the placebo group). Few patients were vaccinated against pneumococcus disease (3.8%). Few patients received antibiotics during the 6 months previously to the study, nor received antiviral treatment. A total of 28 patients (4.1%) (4.4% in the Oscillococcinum® group and 3.9% in the placebo group) had used Oscillococcinum® during the 12 months prior to study. Most patients received a concomitant treatment prior to the study (80.9%), mainly paracetamol (532 patients/ 680, 78.2%) (79.5% in the Oscillococcinum® group and 76.9% in the placebo group) (c.f. statistical report).

Symptoms severity at baseline:

Most patients had 3 or 4 different systemic symptoms at baseline (Oscillococcinum® group: 89.2%, placebo group: 91.1%) and 2 or 3 respiratory symptoms (Oscillococcinum® group: 89.5%, placebo group: 92.3%) (Table S3). The symptoms were considered as moderate in 65.3% of patients (Oscillococcinum® group: 65.2%, placebo group: 65.4%). and severe in 29.4% of them (Oscillococcinum® group: 29.2%, placebo group: 29.6%). Other suspected infectious diseases were tested at baseline; 4 patients were positive to influenza (Oscillococcinum® group: 2 patients and

placebo group: 2 patients), 30 patients positive to COVID 19 (Oscillococcinum® group: 14 patients and placebo group: 16 patients), and no patients positive to Streptotest®.

Table S3 – ILI symptoms and severity at baseline – (FAS, N=680)

		Oscillococcinum® (N=342)	Placebo (N=338)	Total - FAS (N=680)
Global symptoms severity	None	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Mild	19 (5.6%)	17 (5.0%)	36 (5.3%)
	Moderate	223 (65.2%)	221 (65.4%)	444 (65.3%)
	Severe	100 (29.2%)	100 (29.6%)	200 (29.4%)
Systemic symptoms				
Number of systemic symptoms	1	10 (2.9%)	6 (1.8%)	16 (2.4%)
	2	27 (7.9%)	24 (7.1%)	51 (7.5%)
	3	146 (42.7%)	149 (44.1%)	295 (43.4%)
	4	159 (46.5%)	159 (47.0%)	318 (46.8%)
Fever (≥ 37.8 °C)		**217 (63.5%)**	**203 (60.1%)**	**420 (61.8%)**
intensity	None	125 (36.5%)	135 (39.9%)	260 (38.2%)
	Mild [37.8-38.4]	146 (42.7%)	124 (36.7%)	270 (39.7%)
	Moderate [38.5-39]	65 (19.0%)	67 (19.8%)	132 (19.4%)
	Severe ≥39.1	6 (1.8%)	12 (3.6%)	18 (2.6%)
Chills		**323 (94.4%)**	**311 (92.0%)**	**634 (93.2%)**
Severity	None	19 (5.6%)	27 (8.0%)	46 (6.8%)
	Mild	154 (45.0%)	163 (48.2%)	317 (46.6%)
	Moderate	143 (41.8%)	132 (39.1%)	275 (40.4%)
	Severe	26 (7.6%)	16 (4.7%)	42 (6.2%)
Fever/chill	**Yes**	**329 (96.2%)**	**320 (94.7%)**	**649 (95.4%)**
	No	13 (3.8%)	18 (5.3%)	31 (4.6%)
Headache		**326 (95.3%)**	**326 (96.4%)**	**652 (95.9%)**
Severity	None	16 (4.7%)	12 (3.6%)	28 (4.1%)
	Mild	108 (31.6%)	129 (38.2%)	237 (34.9%)
	Moderate	183 (53.5%)	162 (47.9%)	345 (50.7%)
	Severe	35 (10.2%)	35 (10.4%)	70 (10.3%)
Myalgia		**318 (93.0%)**	**318 (94.1%)**	**636 (93.5%)**
Severity	None	24 (7.0%)	20 (5.9%)	44 (6.5%)
	Mild	115 (33.6%)	124 (36.7%)	239 (35.1%)
	Moderate	166 (48.5%)	159 (47.0%)	325 (47.8%)
	Severe	37 (10.8%)	35 (10.4%)	72 (10.6%)
Malaise		**165 (48.2%)**	**173 (51.2%)**	**338 (49.7%)**
Severity	None	177 (51.8%)	165 (48.8%)	342 (50.3%)
	Mild	82 (24.0%)	90 (26.6%)	172 (25.3%)
	Moderate	79 (23.1%)	78 (23.1%)	157 (23.1%)
	Severe	4 (1.2%)	5 (1.5%)	9 (1.3%)
Respiratory symptoms				
Number of respiratory symptoms	1	36 (10.5%)	26 (7.7%)	62 (9.1%)
	2	109 (31.9%)	118 (34.9%)	227 (33.4%)
	3	197 (57.6%)	194 (57.4%)	391 (57.5%)
Cough		**313 (91.5%)**	**310 (91.7%)**	**623 (91.6%)**
Severity	None	29 (8.5%)	28 (8.3%)	57 (8.4%)
	Mild	111 (32.5%)	115 (34.0%)	226 (33.2%)
	Moderate	175 (51.2%)	167 (49.4%)	342 (50.3%)
	Severe	27 (7.9%)	28 (8.3%)	55 (8.1%)

		Oscillococcinum® (N=342)	Placebo (N=338)	Total - FAS (N=680)
Sore throat		**314 (91.8%)**	**319 (94.4%)**	**633 (93.1%)**
Severity	None	28 (8.2%)	19 (5.6%)	47 (6.9%)
	Mild	91 (26.6%)	95 (28.1%)	186 (27.4%)
	Moderate	186 (54.4%)	192 (56.8%)	378 (55.6%)
	Severe	37 (10.8%)	32 (9.5%)	69 (10.1%)
Shortness of breath		**218 (63.7%)**	**215 (63.6%)**	**433 (63.7%)**
Severity	None	124 (36.3%)	123 (36.4%)	247 (36.3%)
	Mild	119 (34.8%)	136 (40.2%)	255 (37.5%)
	Moderate	92 (26.9%)	72 (21.3%)	164 (24.1%)
	Severe	7 (2.0%)	7 (2.1%)	14 (2.1%)

Study Treatment

First intake was compliant with the study eligibility criteria (should have been taken within 24h after symptoms had appeared) (Oscillococcinum® group: mean: 12.5h and placebo group: 12.4h) (Table S4). Doses of study were taken as prescribed for patients (Oscillococcinum® group: 99.1%, placebo group: 98.8%).

Of the 680 FAS patients, 594 (87.4%) were prescribed paracetamol (Oscillococcinum® group: 85.7% and placebo group: 89.1%). Finally, 163 patients (47.7%) in the Oscillococcinum® group used paracetamol during the study and 177 (52.4%) in the placebo group used paracetamol during the study (c.f. statistical report).

Table S4: Study treatment use (FAS, N=680)

		Oscillococcinum® (N=342)	Placebo (N=338)	Total - FAS (N=680)
Time between intake of the first dose of study treatment and ILI symptoms start (hours)	Analysed number	342	338	680
	Mean (±SD)	12.5 (± 5.8)	12.4 (± 5.9)	12.4 (± 5.9)
	Median	11.7	12	11.9
	Q1;Q3	8.8 ; 17.5	8 ; 16.9	8.4 ; 17.2
	Min;Max	-1 ; 23.7	0 ; 32.4	-1 ; 32.4
Doses of study treatment taken as prescribed	Yes	328 (99.1%)	322 (98.8%)	650 (98.9%)
	No	3 (0.9%)	4 (1.2%)	7 (1.1%)
	Missing	11 -	12 -	23 -
If no, reason	Adverse event	0 (0.0%)	1 (25.0%)	1 (14.3%)
	Withdrawal of consent	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Doctor's decision	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Lack of efficacy	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Unblinding	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Other	3 (100.0%)	1 (25.0%)	4 (57.1%)
	Missing	0 -	2 -	2 -

Efficacy Results

Primary efficacy endpoint

The primary efficacy endpoint, the alleviation of symptoms within 72 hours, occurred in 35.0% of patients in the Oscillococcinum® group (n=93/ 266 patients with a PRO measurement at 72h)) and in 29.7% of patients in the placebo group (n=77/ 259 patients with a PRO measurement at 72h) (Table S5). The test was not statistically significant between the two treatment groups (unilateral test, p-

value=0.10). The study did not allow to demonstrate a superiority of Oscillococcinum® compared to placebo. The Relative Risk (RR) of being improved with Oscillococcinum® compared to placebo was 1.18, 90%CI [0.95 – 1.45].

In the multivariate logistic model presented in Figure S1, adjusted on age, symptoms severity at baseline, use of paracetamol and time of onset of ILI symptoms at baseline, the OR for the Oscillococcinum® group was 1.28 (90% CI [0.94 – 1.75]) and did not show statistically significant difference (p=0.10) compared to the placebo group (155 patients without PRO measurement at 72h excluded from the model).

Additional sensitivity analyses to assess the impact of missing data and of subset population definitions confirmed the results between the two groups in the PP population and in the subset of patients in the statistical report. The alleviation of each symptom separately presented in the statistical report concluded to the same results, while statistical tests did not show a difference between the two groups.

Table S5: Synthesis of the primary efficacy results from the efficacy analysis (FAS, N=680)

			Oscillococcinum® (N=342)	Placebo (N=338)	P-value	P-value
Primary endpoint	**Alleviation of all symptoms at 72h**	Yes	93 (35.0%)	77 (29.7%)	0.10*	0.10**
		No	173 (65.0%)	182 (70.3%)		
		Missing	76 -	79 -		
		RR [90%CI]	**1.18 [0.95 – 1.45]**			

*155 patients without PRO measurement at 72h.; *: Chi-Squared test, one sided; **: CMH, one sided*

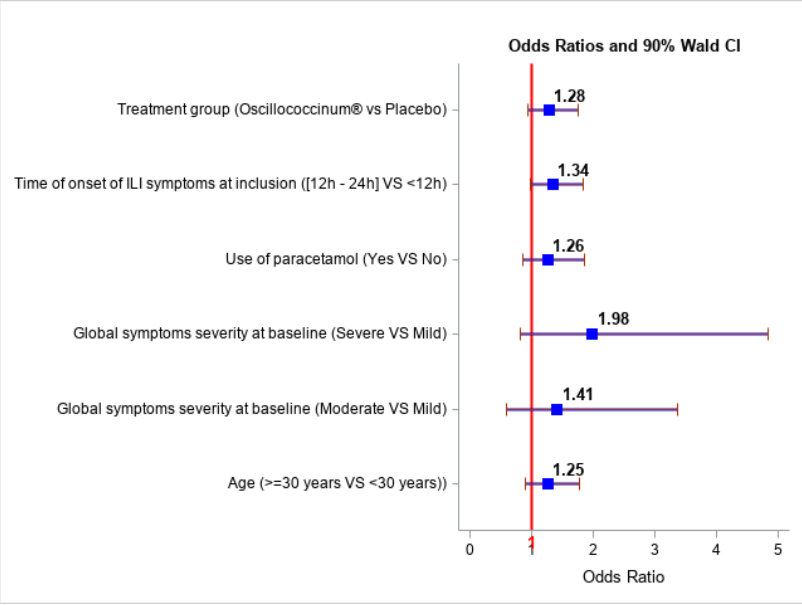

Figure S1 – Result of multivariate logistic model of factors associated with alleviation at 72h of all symptoms present at baseline (FAS population, N=680)

Secondary efficacy endpoints

A summary of the main results regarding the secondary efficacy endpoint analysis is displayed in Table S6. Secondary endpoints did not show statistically significant results between Oscillococcinum® and the placebo. Sensitivity analysis in different population sets confirmed that results were robust and did not vary with the sets of patients analysed.

In term of satisfaction, patients and physician were mainly satisfied and very satisfied with the treatment in both groups with no statistical differences between the groups. Patients were satisfied or very satisfied in 76.4% of cases in the Oscillococcinum® group and in 73.4% of cases in the placebo group (p=0.75) and physicians were satisfied or very satisfied in 82.8% of cases in the Oscillococcinum® group and in 84.0% of cases in the placebo group (p=0.19).

Table S6: Synthesis of the secondary efficacy results from the efficacy analysis (FAS, N=680)

			Oscillococcinum® (N=342)	**Placebo (N=338)**	**P-value**	**P-value**
Secondary endpoints	**Alleviation of all symptoms at 72h maintained over at least 24h**	Yes	12 (12.9%)	12 (15.6%)	0.31*	0.25**
		No	81 (87.1%)	65 (84.4%)		
		Missing	249 -	261 -		
		RR [90%CI]	**0.83 [0.44 – 1.54]**			
	Alleviation of all symptoms at 48h	Yes	62 (23.1%)	61 (22.0%)	0.38*	0.38**
		No	206 (76.9%)	216 (78.0%)		
		Missing	74 -	61 -		
		RR [90%CI]	**1.05 [0.81 – 1.36]**			
	Time to alleviation of symptoms of ILI (days)	Mean (±SD)	7.7 (± 3)	7.5 (± 3.2)	0.43***	
		Median	9.1	9.1		
		Q1-Q3	6.4 - 9.4	5.7 - 9.4		
		Missing	25	21		
	Time to return to usual daily activities (days)	Mean (±SD)	1.7 (± 3.8)	1.8 (± 1.9)	0.02***	
		Median	1	1		
		Q1-Q3	0 - 3	0 - 3		
		Missing	95	89		
	Number of days of absence from work/school (days)	Mean (±SD)	1.7 (± 2.2)	1.8 (± 2.3)	0.51***	
		Median	1	1		
		Q1-Q3	0 - 3	0 - 3		
		Missing	113	105		
	Number of days with sick certificate (days)	Mean (±SD)	1.4 (± 2.1)	1.5 (± 2.1)	0.36***	
		Median	0	0		
		Q1-Q3	0 - 2	0 - 3		
		Missing	113	105		
	Sleep quality (MMRM) *Oscillococcinum® vs Placebo***	Difference of LS means	-0.069		0.59++	
		[95% CI]	[-0.32 ; 0.18]			
		(±SD)	0.13			
	Alleviation of fatigue at 72h	Yes	153 (59.5%)	158 (62.5%)	0.25*	0.24**
		No	104 (40.5%)	95 (37.5%)		
		Missing	85 -	85 -		
		RR [90%CI]	**0.95 [0.85 – 1.07]**			
	Alleviation of nasal congestion at 72h	Yes	113 (44.1%)	116 (45.8%)	0.35*	0.32**
		No	143 (55.9%)	137 (54.2%)		
		Missing	86 -	85 -		
		RR [90%CI]	**0.96 [0.82 – 1.13]**			
	Alleviation of gastro-intestinal disturbances at 72h	Yes	64 (25.1%)	59 (23.3%)	0.32*	0.30**
		No	191 (74.9%)	194 (76.7%)		
		Missing	87 -	85 -		
		RR [90%CI]	**1.08 [0.83 – 1.39]**			
	At least one secondary complication of ILI between D1 and D10	Yes	17 (5.1%)	12 (3.7%)	0.36+	
		No	314 (94.9%)	314 (96.3%)		
		Missing	11 -	12 -		
		Yes	244 (85.3%)	236 (81.7%)	0,24+	

Compliant regarding the use of treatment (according to Physician's assessment)	No Missing	42 (14.7%) 56 -	53 (18.3%) 49 -	
Satisfaction with the treatment according to patient	Satisfied/very satisfied Fairly satisfied Unsatisfied Missing	175 (76.4%) 34 (14.8%) 20 (8.7%) 113 -	171 (73.4%) 39 (16.7%) 23 (9.9%) 105 -	0.75+
Satisfaction with the treatment according to physician	Satisfied/very satisfied Fairly satisfied Unsatisfied Missing	274 (82.8%) 51 (15.4%) 6 (1.8%) 11 -	274 (84.0%) 40 (12.3%) 12 (3.7%) 12 -	0.19+

: (Chi-Squared test, one sided); **: (CMH, one sided);*: Wilcoxon-Mann-Whitney; +Pearson's Chi-square test; ++: ANOVA*

Safety Results

Table S7 summarises the occurrence of AEs. All AEs occurring during the study period and up to 28 days after the last intake of the study medication were considered in the safety analysis. Briefly, 29 (4.3%) patients had at least one AE during the study (Oscillococcinum® group: 13 patients (3.8%); placebo group: 16 patients (4.7%)). No patient experienced SAE. Regarding treatment-related AE (TRAE), there were:

- 2 (0.3%) patients who experienced at least one TRAE (Oscillococcinum® group: 1 patient (0.3%); placebo group: 1 patient (0.3%));
- 1 (0.1%) patient who experienced at least one TRAE leading to permanent treatment discontinuation (Oscillococcinum® group: 0 patient; placebo group: 1 patient (0.3%));
- 0 patient who experienced serious TRAE.

Table S7 - Occurrence of adverse events (AE) according to treatment group (unit=patient) - Safety population

		Oscillococcinum® (N=342)	Placebo (N=338)	Safety population (N=680)	p-value
Patients with at least one:					
Adverse Event (AE)	Yes	13 (3.8%)	16 (4.7%)	29 (4.3%)	0.55
	No	329 (96.2%)	322 (95.3%)	651 (95.7%)	
Treatment related AE (TRAE) (Yes = reasonable possibility)	Yes	1 (0.3%)	1 (0.3%)	2 (0.3%)	1
	No	341 (99.7%)	337 (99.7%)	678 (99.7%)	
AE leading to permanent treatment discontinuation	Yes	0 (0.0%)	1 (0.3%)	1 (0.1%)	0.5
	No	342 (100.0%)	337 (99.7%)	679 (99.9%)	
TRAE leading to permanent treatment discontinuation	Yes	0 (0.0%)	1 (0.3%)	1 (0.1%)	0.5
	No	342 (100.0%)	337 (99.7%)	679 (99.9%)	
If yes, Time between Oscillococcinum initiation and first AE (days)	Missing	0	0	0	
	Analysed number	13	16	29	
	Mean (±SD)	4.5 (± 3)	3.6 (± 3.3)	4 (± 3.1)	0.45
	Median	4	3.5	4	
	Q1-Q3	3 - 5	1 - 5	2 - 5	
	Min-Max	1 - 12	0 - 11	0 - 12	
Patients with at least one: Serious Adverse Event (SAE)	Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
	No	342 (100.0%)	338 (100.0%)	680 (100.0%)	

The most frequent AEs (i.e., those reported by more than 1 patient in the study) were, in decreasing order:

- Sinusitis (Oscillococcinum®: 3 patients (0.9%); placebo: 3 patients (0.9%));
- Bronchitis (Oscillococcinum®: 2 patients (0.6%); placebo: 1 patient (0.3%));
- Diarrhoea (Oscillococcinum®: 2 patients (0.6%); placebo: 2 patients (0.6%));
- Cough (Oscillococcinum®: 2 patients (0.6%); placebo: 2 patients (0.6%));
- Gastroenteritis (Oscillococcinum®: 1 patient (0.3%); placebo: 1 patient (0.3%));
- Abdominal pain upper (Oscillococcinum®: 1 patient (0.3%); placebo: 1 patient (0.3%));
- Asthenia (Oscillococcinum®: 1 patient (0.3%); placebo: 1 patient (0.3%));
- Headache (Oscillococcinum®: 1 patient (0.3%); placebo: 1 patient (0.3%));

The 2 cases of TRAEs were:

- Abdominal pain upper (Oscillococcinum®: 1 patient (0.3%); placebo: 0 patient (0.0%));
- Urticaria (Oscillococcinum®: 0 patient (0.0%); placebo: 1 patient (0.3%));

TRAEs reported in the GOSCI clinical trial were limited to 2 non serious cases including one case of abdominal pain upper and one case of urticaria. No SAE were reported. Other reported AEs were expected in the context of ILI. All AEs were consistent with the use of the study treatment and the management of patients with ILI.

Discussion

Whereas Oscillococcinum® is widely used in many countries, the GOSCI study was designed to provide updated data on the benefit of using the homeopathic medicine in the treatment of ILI and to ensure a robust evaluation following the methodological criteria of the Cochrane review (10-12). To meet these expectations, the definition of ILI used in the study was that of the Official Journal of the European Union (OJEU (1)). Fever was considered when the body temperature was ≥ 37.8 °C (2), and chills were defined as the patient's subjective symptom of feeling feverish or cold. To avoid bias due to patient and physician preferences, suggestions and expectations, this study was conducted as a prospective, double-blind, placebo-controlled trial at multiple study sites in France and Belgium. The sample size was estimated on the basis of the results of previous clinical trials (in particular Papp study, (9)), accounting for 10% of incomplete cases that could not be included in the estimate of the primary endpoint, and assumed the 640 patients needed to be recruited (587 assessable for the primary endpoint).

After three winter seasons of patients' recruitment, the enrolment objective was reached and 680 patients were included in the FAS analysis. Alleviation of all symptoms at 72 hours occurred in 35.0% of patients in the Oscillococcinum® group and in 29.7% of patients in the placebo group, showing a difference of 5.3% in favour of Oscillococcinum®. However, despite this >5 -point difference between the two groups, the result was not statistically significant for the primary endpoint (unilateral test, p-value=0.10). Multivariate analysis showed the same result. This difference remained within the range of results obtained in the previous clinical trials. In fact, in the Papp study (9), the difference between the two groups in terms of " clear improvement " of symptoms reached 10% and the difference in terms of " improvement " reached 5%.

The GOSCI study faced several limitations and difficulties. The first and main difficulty was the management of patient recruitment by general practitioners during the COVID pandemic period, when physicians had to focus on managing the pandemic and its consequences and vaccinations. Although we were able to show that few COVID-positive patients were recruited into GOSCI, the co-occurrence of the pandemics with the study had an impact on patients' recruitment, which had to be extended over three winter seasons instead of one, and on the final number of patients recruited into the study. The second issue was the proportion of patients who did not correctly and completely complete the PRO required to estimate the primary outcome. The protocol anticipated that 10% of PROs could not be analysed. In the end, the primary endpoint analysis could be performed on 525 patients (155 missing data at 72 hours) instead of the expected 587 files (77% of the 680 enrolled patients). Although it was found that patients with missing data at 72h did not differ from patients with data, the loss of patients evaluable at 72h had an impact on the statistical power of the study and did not allow the initial 7% difference between the two groups to be detected. Based on these results (a 5.3% positive improvement in favour of Oscillococcinum® and a 23% attrition rate), the trial should have enrolled more than 1000 patients to meet its primary objective.

Although the study did not show superiority of Oscillococcinum® over placebo, several lessons were learned regarding the needed sample size and the PRO completion rate for potential future studies, as well as the high level of patients and physicians' satisfaction with the treatment and the confirmed high degree of tolerability.

Conclusion

The GOSCI study was a robust and well-designed clinical trial to assess the efficacy of Oscillococcinum® in alleviating ILI symptoms. Despite a difference of 5.3% in favour or Oscillococcinum® in the primary endpoint of symptom relief at 72 hours, the study did not demonstrate statistical superiority of the treatment, but several lessons were learned regarding the needed sample size and the PRO completion rate for potential future studies, as well as the high level of patients' and physicians' satisfaction with the treatment and the confirmed high level of tolerability.

List of Abbreviations

%	Percentage
°C	Degree Celsius
AE	Adverse Event
ANOVA	Analysis Of Variance
BMI	Body Mass Index
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRO	Contract Research Organisation
D_i	Day I (D0: Day 0=Inclusion / D10: Day 10)
FAS	Full Analysis Set
FPFV	First Patient First Visit
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ILI	Influenza-like illness
IQR	Inter Quartile Range
IRB	Independent Review Board
ITT	Intention to Treat
IWRS	Interactive Web Response System
Kg	kilogram
LPFV	Last Patient First Visit
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
Min-max	Minimum-Maximum
MMRM	Mixed Model for Repeated Measures
NR	Not Related
OR	Odd Ratio
PP	Per Protocol
PRO	Patient-Reported Outcome
PT (MedDRA)	Preferred Term (MedDRA)
Q1-Q3	First and Third quartile (25% and 75% of patients)
RR	Relative Risk
SAE	Serious Adverse Event
SD	Standard Deviation
SOC (MedDRA)	System Organ Class (MedDRA dictionary)
TRAE	Treatment-Related Adverse Event

List of Investigators

N°RRPS investigator	N° site	Name	Forename	Postal Code	Town
10002461803	1	ROSUNEE	CHABEENDRANATH	67000	STRASBOURG
10001982827	2	MINGAM	STÉPHANE	76620	LE HAVRE
10002417524	4	TOLEDANO	JUDAH	67000	STRASBOURG
10001225134	5	HOZE	MICHEL	94300	VINCENNES
10003362521	6	DASSA	GÉRARD	13800	ISTRES
10002710614	7	DELABROYE	STÉPHANE	79320	MONCOUTANT
10002389186	8	FERRETTI	JEAN	88390	LES FORGES
10000560267	9	LABREGERE	ARNAUD	75002	PARIS
10003254348	10	RAZAFY	JEANNOT	27160	BRETEUIL SUR ITON
10003998217	11	BARANES	CHARLES	75020	PARIS
10000320258	13	SEBBAH	ANDRÉ PROSPER	75015	PARIS
10100199206	14	BLIN	CÉCILIA	56000	VANNES
10003106845	15	BLOT	ETIENNE	76000	ROUEN
10002529013	61	BARAT	VERONIQUE	44115	HAUTE GOULAINE
10002913456	296	DEFREYN	FREDERIC	31810	VERNET
10003878187	633	MAALEJ	ADNENE	55200	COMMERCY
10002295441	766	PERU	CHRISTOPHE	59155	FACHES THUMESNIL
10100343200	875	SAADA	ARNAUD	91300	MASSY
10003298519	1013	ZEGGAGH	AHMED	06400	CANNES
10002783784	1016	LE MOUEL	STÉPHANE	40180	HINX
10001863538	1061	MERCIER	INNA	75006	PARIS
10001426435	1127	PLATEK	ANDRZEJ	91250	TIGERY
10004027503	1078	BRESCIANI	STEFANIA	20145	SOLENZARA
10002728821	2095	LASSIME	JEROME	16360	BAIGNES STE RADEG
	4688	BUNTINX	ELS	3570	ALKEN
10002179223	2841	BOISSELIER	CHRISTOPHE	21000	DIJON
10002313657	3560	CHEVALIER	AURORE	59242	TEMPLEUVE
10004413745	2959	BLOCK	FLORIAN	57600	FORBACH
10002241940	3059	SPECHT	LIONEL	59130	LAMBERSART
10001821296	3066	GROSSEMY	XAVIER	80080	AMIENS
10003849832	3067	MONTELS	MICHEL	33770	SALLES
10002238532	3068	DELSART	DOMINIQUE	59235	BERSEE
10002898715	3079	RIGAUD	NORBERT	82360	LAMAGISTERE
10001877785	3083	DAGES	LAURENCE	27504	PONT AUDEMER CEDEX
10002044427	3094	MEME	BRUNO	37520	LA RICHE
10003265419	3097	PATRON	BRUNO	05000	GAP
10002785995	3099	RENAULT	ERIC	40480	VIEUX BOUCAU LES BAINS

10001957769	3164	CAULIEZ	BRUNO	76100	ROUEN
10101479185	3556	HANEL	PAULINE	59230	SAINT AMAND LES EAUX
	4689	HELSEN	CAROLINE	2400	MOL
10004399969	4095	MARCO BOTTI	VANESSA	13013	MARSEILLE
10001901718	3555	MARTIN	MARC	76130	MONT SAINT-AIGNAN
10002041290	4000	MERCIER	PIERRE	37000	TOURS
10100096220	4699	MERLIN	ANNE MARIE	59283	RAIMBEAUCOURT
	4666	PONLOT	JEAN-LUC	5300	LANDENNE
10100097137	4700	PUJOL-NOZERES	STÉPHANIE	33700	MERIGNAC
	3559	SALINGUE	CHARLOTTE	59160	LOMME
	4697	SCHUSTER	MARIELLE	6840	HAMIPRE
	4684	VAN RENTERGHEM	DIRK	9840	DE PINTE
10100181045	3558	VUYLSTEKER	LAURIE	59235	BERSEE

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