



Efficacy and safety of Ergoferon versus oseltamivir in adult outpatients with seasonal influenza virus infection: a multicenter, open-label, randomized trial



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SUMMARY

Objectives: Ergoferon is an antiviral complex drug containing released-active forms of antibodies to interferon gamma, CD4, and histamine. Its efficacy and safety in the treatment of acute respiratory viral infections has been reported previously. The aim of this study was to compare Ergoferon with oseltamivir.

Methods: A multicenter, open-label, randomized controlled trial of patients aged 18 to 65 years, who had tested positive for influenza A or B antigens, was performed. A total of 156 patients were enrolled as the intention-to-treat population; these patients were assigned randomly to receive either Ergoferon or oseltamivir ($n = 78$ in each group).

Results: The percentage of patients achieving a normal body temperature ($\leq 37.0^{\circ}\text{C}$) following 5 days of treatment did not differ significantly between the groups. The mean duration of fever in the Ergoferon and oseltamivir groups was 2.1 ± 1.5 days and 2.3 ± 1.6 days, respectively ($p = 0.01$). The average time to the resolution of influenza symptoms was approximately 3 days, with no significant between-group difference. Total quality of life scores were similar in the two groups following 5 days of drug administration. The incidence of adverse events did not differ significantly between the groups, nor were there any serious adverse events.

Conclusions: Ergoferon and oseltamivir were equally effective and safe in adult outpatients with seasonal influenza A or B virus infection.

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1. Introduction

Influenza is an infection affecting populations worldwide caused by highly contagious, epidemically aggressive and mutagenic viruses.^{1,2} More than 200 000 hospitalizations and an average of 25 470 deaths occur in the USA each year due to seasonal influenza.^{3,4} Resistance of influenza A viruses to adamantanes increased globally in 2003 and has since become universal for circulating influenza A(H1N1) and A(H3N2)

subtypes.⁵ The mainstay of influenza therapy therefore consists primarily of the neuraminidase inhibitors oseltamivir and zanamivir, which are licensed widely throughout the world.⁶

The pandemic caused by the 2009 influenza A(H1N1) virus, as well as the increase in viral strains with resistance to neuraminidase inhibitors, has underscored the need for better treatment options for hospitalized patients and outpatients.² A drug with a high efficacy-to-safety ratio that is able to overcome the virus resistance and that also has advantages from a pharmacoeconomic point of view could be attractive as a treatment option. Ergoferon, a drug containing released-active forms of antibodies to interferon gamma (IFN- γ), CD4, and histamine, and whose efficacy and safety against influenza and acute respiratory viral infections

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has been shown previously, could be considered one such drug.^{7–9} Released-active forms of antibodies are produced on the basis of a novel technology (US Patent 8,535,664 B2, 2013) and share a common feature – the ability to modify the initial substance (or biological molecules which are structurally similar to the initial substance) by changing its spatial structure, resulting in alterations to its physical, chemical, and biological properties.¹⁰ The efficacy and safety of these drugs has been studied extensively and has been proven in different experimental and clinical studies.^{11–18}

The superiority of Ergoferon over placebo has been shown in double-blind, placebo-controlled studies in adults and children with acute upper respiratory viral infections and influenza.^{7–9} The objective of this clinical trial was to compare the efficacy and safety of Ergoferon with oseltamivir in the treatment of seasonal influenza in adults.

2. Methods

2.1. Study overview

This study was a multicenter, open-label, randomized controlled trial performed in 12 medical institutions in Russia from February 2011 to April 2014. This period succeeded the emergence of the 2009 pandemic influenza A/H1N1 virus (pH1N1). Furthermore, the influenza morbidity in Russia was low during the study period. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice and was approved by the institutional review boards and the national research ethics committee. Signed informed consent was obtained from all participants prior to enrollment. Due to the open design of the trial, the interim analysis was performed in 2012 to compare the efficacy of the study treatments.¹⁹

Eligible patients were assessed by physicians on days 1, 3, and 7 in the outpatient departments of the study centers involved (see **Supplementary Material**).

2.2. Patient selection

The study enrolled adults aged 18 to 65 years who presented to hospital within 24 h of the onset of influenza symptoms and who had an axillary temperature of ≥ 37.8 °C at enrollment plus one or more flu-related non-specific symptoms (headache, myalgia, joint pain, sweats and/or chills, malaise, or fatigue) and one or more respiratory symptoms (cough, sore throat, or nasal symptoms). Infection with influenza A or B virus was confirmed by rapid antigen testing (QuickVue Influenza A+B test; Quidel Corporation, San Diego, CA, USA).

Individuals were excluded from the study if they had an exacerbation or decompensation of a chronic disease that would affect their ability to participate in the clinical trial, chronic renal insufficiency, vaccination against influenza prior to epidemic season onset, medical history of polyvalent allergy, allergy/intolerance to any of the components or medications used in the treatment, suspected or known bacterial infection, a condition requiring antibacterial therapy, or HIV disease. They were also excluded if they were receiving systemic therapy with steroids or other immunosuppressants, or had a history of alcohol or drug abuse. Women were required to have a negative urine pregnancy test before drug administration. Breastfeeding women were not eligible for participation.

2.3. Patient assessment

Anterior nose and posterior pharyngeal throat swabs were taken at baseline and assessed with the QuickVue Influenza A+B kit for rapid diagnostic testing for influenza.

The participants were monitored for a total of 7 days, with hospital visits scheduled for days 1, 3, and 7. All visits included the measurement of axillary temperature, a physical examination, evaluation of influenza symptoms by the physician, and assessment of the intake of concomitant therapies. The laboratory analyses (hematology, blood chemistry, and urinalysis) were performed on days 1 and 7. The severity of each influenza symptom was scored by the physician on a symptom severity scale (0 = no symptoms; 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms). Baseline and end-of-treatment quality of life assessments were based on the first five points of the European Quality of Life Scale (EuroQoL, EQ5D); baseline and end-of-treatment self-reported 'health-related quality of life' estimates were obtained using a visual analogue health-rating scale (EQ5D, point 6). The assessment of compliance with the study therapies was done on the last visit (day 7).

Axillary temperature measurements were taken by the study participants twice daily using a digital thermometer and recorded on a diary card. The names and doses of concomitant medications taken (other than the two drugs specifically assessed during the study) were recorded in the patient diary.

Safety assessments included examiner-reported adverse events (AEs) and self-reported AEs during the 5 days of treatment and the following 30 days, as well as abnormal laboratory findings on day 7.

2.4. Treatment

The participants were assigned randomly to receive Ergoferon (group 1) or oseltamivir (group 2). Randomization occurred at the time of study entry by telephone contact with an automated service (an interactive voice randomization system based on a random number generator).

Ergoferon (OOO NPF 'Materia Medica Holding', Russia) was administered according to the following regimen: on day 1, five tablets were taken in the first 2 h (one tablet every 30 min), followed by three more tablets regularly spaced during the rest of the day. From day 2 through day 5, one tablet was administered three times daily. The efficacy and safety of this specific drug regimen has been assessed and proven in previous clinical trials.^{7,8}

Each tablet of Ergoferon contains microcrystalline cellulose (30 mg), magnesium stearate (3 mg), and lactose monohydrate (267 mg) saturated with a mixture of affinity purified rabbit polyclonal antibodies to IFN- γ , antibodies to histamine, and antibodies to CD4 receptor, which had previously undergone a process of gradual reduction of their initial concentration (2.0–2.5 mg/ml) by 10^{24} times at least (mixture of dilutions 100^{12} , 100^{30} , and 100^{50}). This technology conforms to the approach described in the European Pharmacopoeia (general monographs 1038 and 2371) and allows the use of active pharmaceutical ingredients – the released-active form of the above-mentioned antibodies – based on a novel patented biotechnological platform (US Patent 8,535,664 B2, 2013). The initial forms of the antibodies were produced in accordance with the current EU requirements of Good Manufacturing Practice for starting materials (EU Directive 2001/83/EC, as amended in Directive 2004/27/EC) by AB Biotechnology (Edinburgh, UK). The fact that properties of the active pharmaceutical ingredients are based primarily on the technological process of their preparation⁹ determines their crucial difference from homeopathic therapy based on other common features (law of similarity, individual hyperergic reactions, and specific methodological principles of personalized indication).

Oseltamivir (Tamiflu; F. Hoffmann-La Roche, Ltd) was administered at a dose of 75 mg orally twice daily for 5 days; this is the recommended dosing regimen for adults. Tamiflu was obtained from a licensed wholesaler (SIA International Ltd).

The following concomitant medications were permitted during the study: antipyretic/non-steroidal anti-inflammatory drugs (NSAIDs) (only for patients with a body temperature $>38.5^{\circ}\text{C}$), decongestants, drugs for obstructive airway diseases, cough suppressants, expectorants, mucolytics, and medications for the treatment of underlying chronic conditions. The use of other antivirals (except Ergoferon and oseltamivir), antihistamines, antibacterials, and interferons was not permitted. The use of NSAIDs and other medications for symptom relief was recorded by the study researchers (physicians) on the case record form and by the patient on a diary card.

2.5. Efficacy endpoints

The percentage of patients with a body temperature $\leq 37.0^{\circ}\text{C}$ following the 5-day treatment was used as the primary efficacy endpoint.

The secondary efficacy endpoints were: (1) mean body temperature; (2) flu-related non-specific and respiratory symptom severity score; (3) mean duration of fever; (4) time to treatment-associated resolution of influenza symptoms; (5) rates of antipyretic/NSAID use per patient during days 1 to 5 of drug administration; (6) changes in patient quality of life (total EQ5D scores) and self-reported 'health-related quality of life' estimates between days 1 and 7; and (7) the percentage of examiner-reported worsening of illness or complications requiring antibacterial therapy during the three medical visits.

2.6. Statistical methods

The study was based on a non-inferiority design. Sample size calculations were based on assumed between-group equality of patient proportions with body temperature $\leq 37.0^{\circ}\text{C}$ for each of the five treatment days. The level of type I error was set at 5% and the statistical power of the analysis at 80%. A one-tailed Z-test was used. Assuming the most conservative hypothesis that the proportions of patients with body temperature $\leq 37.0^{\circ}\text{C}$ in the groups were distributed 50% versus 50%, the minimum sample size required was estimated to be 78 patients in each group. Overall, 156 patients, 78 in each group, were evaluated in this study.

2.6.1. Efficacy analysis

The intention-to-treat (ITT) and per-protocol (PP) analyses were performed in accordance with the current guidelines for evaluating drug efficacy in a clinical non-inferiority trial.²⁰

Patient proportions were compared using frequency analysis (Chi-square test or Fisher's exact test) and Wald Z-statistics. For the comparison of means, a modified paired Student *t*-test was used with the calculation of the confidence interval for differences between sample means. For multiple comparisons, the adaptive Holm procedure was used (the type I error (*p*-value) used to describe the outcomes was adjusted using this method).

2.6.2. Safety analysis

Treatment safety in both groups was assessed in all enrolled and randomized patients who received at least one dose of Ergoferon ($n = 81$) or oseltamivir ($n = 80$).

All recorded AEs, vital signs, clinical laboratory parameters, and physical examination findings were listed, tabulated, and summarized according to the treatment group. The documented AEs were categorized by organ system, preferable terms, severity, and treatment relatedness as determined by the physician.

3. Results

3.1. Patient demographics and baseline characteristics

A total of 161 patients aged 18 to 60 years were enrolled in the study, 81 in group 1 (Ergoferon) and 80 in group 2 (oseltamivir). The date of the first patient enrollment was February 28, 2011; the date on which the last patient completed participation was April 21, 2014.

Five randomized patients (three in group 1 and two in group 2) were excluded from the full analysis owing to a failure to satisfy the major entry criteria (eligibility violations) (Figure 1). Eligibility violations were the following: absence of the documented axillary temperature of $\geq 37.8^{\circ}\text{C}$ at enrollment ($n = 2$ in group 1; $n = 1$ in group 2) or any flu-related symptoms ($n = 1$ in group 1; $n = 1$ in group 2). The rest of the participants ($n = 156$) constituted the ITT set analyzed. Treatment outcomes in this set (78 patients per group) were considered for ITT analysis of efficacy.

In addition, nine patients (three patients in group 1 and six patients in group 2) had substantial protocol violations: absence of the patient diary ($n = 1$ in group 1; $n = 1$ in group 2); temperature gaps in the patient diary for ≥ 1 day ($n = 1$ in group 1; $n = 2$ in group 2); omissions in the case record form ($n = 1$ in group 1; $n = 1$ in group 2). In group 2, two additional participants required the administration of non-permitted medications (antibacterials) on day 4. Hence, the PP analysis set included 147 patients: 75 in group 1 and 72 in group 2.

Basic demographic and clinical parameters (day 1) were comparable between the treatment groups (Tables 1, 3–5). The mean patient age was 34.7 ± 12.1 years (ranging from 18 to 59 years); female patients made up 65% of the study population. The majority of patients presented with typical influenza symptoms (e.g. fever, headache, myalgia) and a predominance of non-specific over respiratory symptoms. On day 1, the mean body temperature was $38.2 \pm 0.4^{\circ}\text{C}$ in group 1 and $38.3 \pm 0.4^{\circ}\text{C}$ in group 2 in the ITT set, and $38.3 \pm 0.4^{\circ}\text{C}$ in both groups in the PP set. All patients in both groups complained of moderate to severe headache, chills, fatigue, muscle pain, and malaise. The mean severity score of flu-related non-specific symptoms on day 1 was 18.8 ± 6.2 (19.0 ± 6.7) in group 1 and 18.6 ± 6.2 (18.6 ± 6.3) in group 2 (hereinafter, ITT analysis data are presented first and PP analysis data are given in brackets). The respiratory symptoms score did not differ significantly between the groups: 6.1 ± 3.7 (6.1 ± 3.7) in group 1 and 5.9 ± 3.7 (5.9 ± 3.6) in group 2; these mostly represented moderate symptoms, such as nasal congestion and sore throat.

More than 30% of patients had different underlying chronic conditions that were not reasons for exclusion (see **Supplementary Material**, Table S1). Most of the patients in both groups received additional permitted concomitant medications (see **Supplementary Material**, Table S2). Neither the percentage of patients with underlying chronic diseases nor the percentage of patients receiving any additional permitted concomitant medication differed significantly between the groups.

3.2. Primary efficacy endpoints

The ITT analysis showed an effect of Ergoferon that was comparable to that of oseltamivir for the 5 days of treatment: 19% of patients in group 1 achieved a normal morning body temperature ($\leq 37.0^{\circ}\text{C}$) as early as day 2 (versus 10% in group 2), 46% of patients in group 1 had a normalized body temperature on day 3 (versus 42% in group 2), and 81% of patients in group 1 had a normalized body temperature on day 5 (versus 71% in group 2) (Table 2). At treatment completion (day 6), all patients in group 1 reported a normal morning body temperature (versus 92% in group 2).

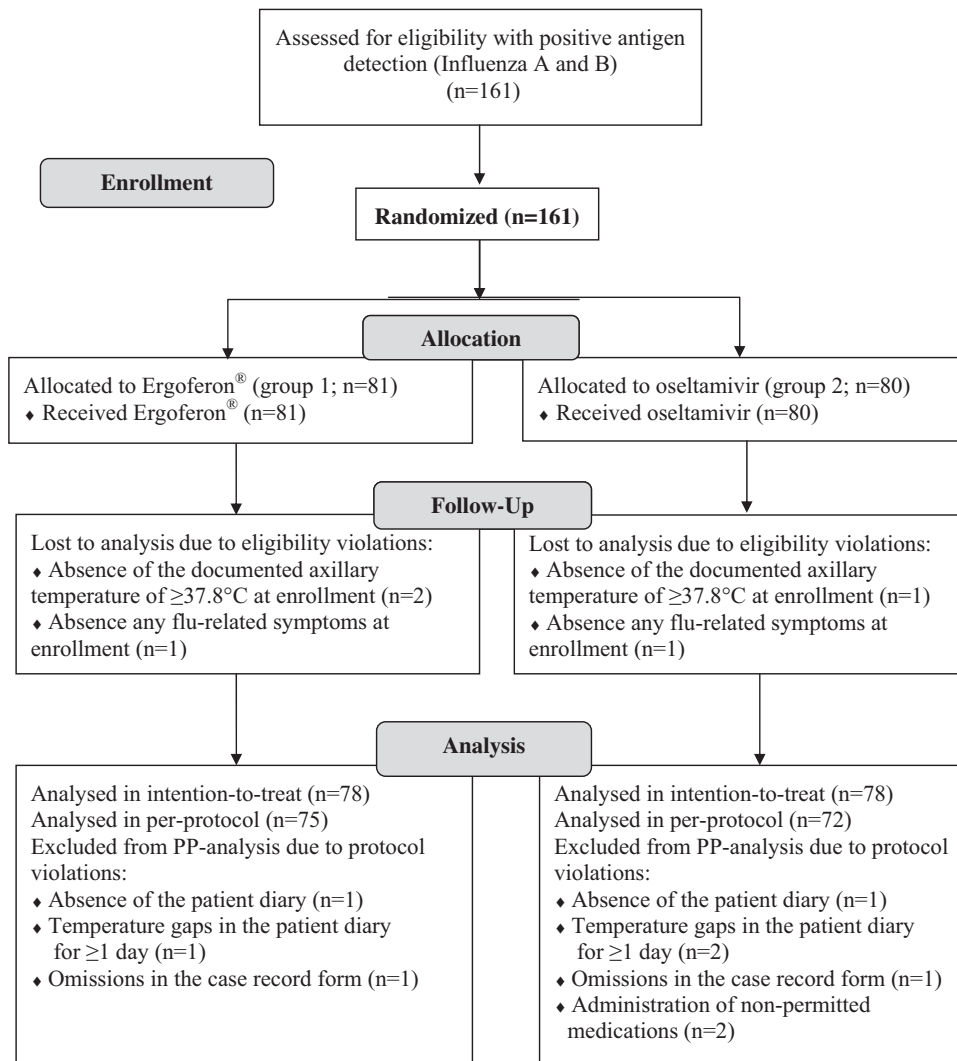


Figure 1. Study design flow diagram.

Table 1
Demographic characteristics of the study participants^a

No.	Variable	Group 1	Group 2	Statistics ^b
1	Age (years), mean ± SD (range)			
	Total set (81/80) ^c	34.5 ± 11.6 (18–59)	34.9 ± 12.6 (18–58)	$t = 0.2; p = 0.84$
	ITT (78/78) ^c	34.2 ± 11.7 (18–59)	35.0 ± 12.7 (18–58)	$t = 0.41; p = 0.68$
	PP (75/72) ^c	34.4 ± 11.7 (18–59)	35.5 ± 12.5 (18–58)	$t = 0.58; p = 0.56$
2	Sex, n (%)			
	Total set (81/80) ^c			
	Male	32 (40)	25 (31)	$\chi^2 = 1.2; p = 0.27$
	Female	49 (60)	55 (69)	
	ITT (78/78) ^c			
	Male	31 (40)	24 (31)	$\chi^2 = 1.4; p = 0.24$
Female	47 (60)	54 (69)		
PP (75/72) ^c				
Male	30 (40)	23 (32)	$\chi^2 = 1.03; p = 0.31$	
Female	45 (60)	49 (68)		

ITT, intention-to-treat analysis; PP, per-protocol analysis.

^a Results are presented as the mean ± standard deviation, or number (percentage).

^b The Statistics column shows the results of the Student *t*-test (section 1) and frequency analysis (section 2).

^c The number of patients in group 1/number of patients in group 2.

The percentage of patients with a normal evening body temperature ($\leq 37.0^\circ\text{C}$) in group 1 was 41% by day 3, 68% by day 4, and 85% by the end of day 5. Group 2 patients had nearly identical values (42%, 69%, and 86%, respectively).

The PP analysis showed similar normalization rates for morning and evening body temperatures in both groups (Table 2).

The ITT (PP) analysis demonstrated consistent results, which suggests that the two study treatments have comparable therapeutic effects (Table 2).

3.3. Secondary efficacy endpoints

The ITT (PP) analysis of mean body temperature showed that the increased baseline values fell to $37.0 \pm 0.5^\circ\text{C}$ by day 3 in both groups and remained consistently below 37.0°C over the subsequent days of observation (Table 3). Statistical analysis showed mean values of fever in group 1 falling within the acceptable ‘ δ ’ limits established for treatment outcomes in group 2 (ITT analysis: $\Delta^\circ = 0.01$, 95% confidence interval (CI) < 0.14 , $t = -2.5$, $p = 0.007$; PP analysis: $\Delta^\circ = 0.005$, 95% CI < 0.14 , $t = -2.4$, $p = 0.008$), confirming the comparable efficacy of the two drugs (Table 3).

The ITT analysis showed more than a two-fold reduction in flu-related non-specific symptom severity score in group 1 on the third day, i.e., 9.2 ± 5.0 (versus 7.7 ± 4.4 in group 2) (Table 4). On the last day of observation (day 7), the mean severity score in the Ergoferon

Table 2
Percentages of patients with a body temperature $\leq 37.0^\circ\text{C}$ during the study period

Treatment day		ITT analysis			PP analysis		
		Group 1 (n = 78)	Group 2 (n = 78)	Statistics ^a	Group 1 (n = 75)	Group 2 (n = 72)	Statistics ^a
1	Morning	0%	1%	$\Delta = -1\%$ (-5% to 2%) $Z = 13.7$; $p < 0.001$	0%	1%	$\Delta = -1\%$ (-5% to 3%) $Z = 12.5$; $p < 0.001$
	Evening	4%	1%	$\Delta = 3\%$ (-4% to 9%) $Z = 8.4$; $p < 0.001$	4%	1%	$\Delta = 3\%$ (-4% to 9%) $Z = 8.0$; $p < 0.001$
2	Morning	19%	10%	$\Delta = 9\%$ (-3% to 21%) $Z = 4.9$; $p < 0.001$	19%	10%	$\Delta = 9\%$ (-4% to 21%) $Z = 4.8$; $p < 0.001$
	Evening	14%	15%	$\Delta = -1\%$ (-14% to 11%) $Z = 3.1$; $p = 0.001$	15%	15%	$\Delta = -1\%$ (-14% to 12%) $Z = 3.1$; $p = 0.001$
3	Morning	46%	42%	$\Delta = 4\%$ (-13% to 21%) $Z = 2.8$; $p = 0.002$	47%	43%	$\Delta = 4\%$ (-14% to 21%) $Z = 2.7$; $p = 0.003$
	Evening	41%	42%	$\Delta = -1\%$ (-18% to 15%) $Z = 2.2$; $p = 0.014$	41%	43%	$\Delta = -2\%$ (-19% to 16%) $Z = 2.1$; $p = 0.019$
4	Morning	81%	71%	$\Delta = 10\%$ (-4% to 25%) $Z = 4.2$; $p < 0.001$	80%	75%	$\Delta = 5\%$ (-10% to 20%) $Z = 3.4$; $p < 0.001$
	Evening	68%	69%	$\Delta = -1\%$ (-17% to 15%) $Z = 2.3$; $p = 0.009$	68%	72%	$\Delta = -4\%$ (-20% to 12%) $Z = 1.9$; $p = 0.028$
5	Morning	95%	83%	$\Delta = 12\%$ (1% to 22%) $Z = 6.2$; $p < 0.001$	95%	83%	$\Delta = 11\%$ (-0% to 23%) $Z = 5.9$; $p < 0.001$
	Evening	85%	86%	$\Delta = -1\%$ (-14% to 11%) $Z = 3.1$; $p = 0.001$	84%	88%	$\Delta = -4\%$ (-16% to 9%) $Z = 2.6$; $p = 0.004$
6	Morning	100%	92%	$\Delta = 8\%$ (0% to 15%) $Z = 8.8$; $p < 0.001$	100%	92%	$\Delta = 8\%$ (1% to 16%) $Z = 8.3$; $p < 0.001$
	Evening	94%	96%	$\Delta = -3\%$ (-11% to 6%) $Z = 4.6$; $p < 0.001$	93%	96%	$\Delta = -3\%$ (-11% to 6%) $Z = 4.3$; $p < 0.001$

ITT, intention-to-treat analysis; PP, per-protocol analysis.

^a The Statistics column shows the results of the frequency analysis (non-inferiority Wald test) with 95% confidence intervals in parentheses.

Table 3
Body temperature on days 1, 3, and 7^a

Day	ITT analysis			PP analysis		
	Group 1 (n = 78)	Group 2 (n = 78)	Statistics ^b	Group 1 (n = 75)	Group 2 (n = 72)	Statistics ^b
1	38.2 ± 0.4	38.2 ± 0.4	$\Delta^\circ = 0.0$; 95% CI < 0.08 $t = -3.6$; $p = 0.0002$	38.3 ± 0.4	38.3 ± 0.4	$\Delta^\circ = 0.0$; 95% CI < 0.08 $t = -3.5$; $p = 0.0003$
3	37.0 ± 0.5	37.0 ± 0.5	$\Delta^\circ = 0.01$; 95% CI < 0.14 $t = -2.5$; $p = 0.007$	37.0 ± 0.5	37.0 ± 0.5	$\Delta^\circ = 0.005$; 95% CI < 0.14 $t = -2.4$; $p = 0.008$
7	36.5 ± 0.2	36.6 ± 0.3	-	36.5 ± 0.2	36.6 ± 0.3	-

ITT, intention-to-treat analysis; PP, per-protocol analysis; CI, confidence interval.

^a Results are presented as the mean ± standard deviation.

^b The Statistics column shows the results of the Student *t*-test modified for comparability (non-inferiority) testing. Δ° is the mean difference between group 1 (Ergoferon) and group 2 (oseltamivir). The *p*-value stands for type I error.

Table 4
Flu-related non-specific symptom severity scores on days 1, 3, and 7^a

Day	ITT analysis			PP analysis		
	Group 1 (n = 78)	Group 2 (n = 78)	Statistics ^b	Group 1 (n = 75)	Group 2 (n = 72)	Statistics ^b
1	18.8 ± 6.6	18.6 ± 6.2	$\Delta = 0.2$; 95% CI < 1.9 $t = -2.7$; $p = 0.003$	19.0 ± 6.7	18.6 ± 6.3	$\Delta = 0.4$; 95% CI < 2.1 $t = -2.5$; $p = 0.007$
3	9.2 ± 5.0	7.7 ± 4.4	$\Delta = 1.5$; 95% CI < 2.8 $t = -2.0$; $p = 0.025$	9.2 ± 5.1	7.8 ± 4.3	$\Delta = 0.45$; 95% CI < 2.8 $t = -2.0$; $p = 0.02$
7	2.4 ± 2.9	2.0 ± 2.5	$\Delta = 0.4$; 95% CI < 1.1 $t = -5.9$; $p < 0.0001$	2.3 ± 2.7	1.9 ± 2.3	$\Delta = 0.39$; 95% CI < 1.1 $t = -6.3$; $p < 0.0001$

ITT, intention-to-treat analysis; PP, per-protocol analysis; CI, confidence interval.

^a Results are presented as the mean ± standard deviation.

^b The Statistics column shows the results of the Student *t*-test modified for comparability (non-inferiority) testing. Δ is the mean difference between group 1 (Ergoferon) and group 2 (oseltamivir). The *p*-value stands for type I error.

group was 2.4 ± 2.9 (versus 2.0 ± 2.5 in the oseltamivir group). The PP analysis yielded almost identical values (Table 4).

The respiratory symptom scores were significantly reduced on treatment day 3 and this reduction was similar in the two groups (for both ITT and PP data). At the completion of treatment, some patients in both groups reported 'residual' catarrhal symptoms, as shown by the mean severity score of over 1.0 (Table 5).

The mean duration of fever was 2.1 ± 1.5 (2.1 ± 1.4) days in group 1 versus 2.3 ± 1.6 (2.3 ± 1.6) days in group 2. This variable was similar in the two groups ($p = 0.01$ ($p = 0.002$)) (Table 6).

The analysis of time to treatment-associated resolution of influenza symptoms showed that the flu-related non-specific symptoms had resolved at 2.7 ± 2.2 days in group 1 and at 2.4 ± 2.1 days in group 2, whereas the improvement in respiratory

Table 5
Respiratory symptom severity scores on days 1, 3, and 7^a

Day	ITT analysis			PP analysis		
	Group 1 (n=78)	Group 2 (n=78)	Statistics ^b	Group 1 (n=75)	Group 2 (n=72)	Statistics ^b
1	6.1 ± 3.7	5.9 ± 3.7	Δ = 0.2; 95% CI <1.2 t = 2.1; p = 0.02	6.1 ± 3.7	5.9 ± 3.6	Δ = 0.2; 95% CI <1.2 t = -2.1; p = 0.02
3	4.3 ± 2.4	3.9 ± 2.7	Δ = 0.4; 95% CI <1.1 t = -2.7; p = 0.004	4.3 ± 2.4	4.0 ± 2.7	Δ = 0.3; 95% CI <1.0 t = -2.8; p = 0.003
7	1.3 ± 1.5	1.4 ± 1.9	Δ = -0.1; 95% CI <0.4 t = -5.8; p < 0.0001	1.3 ± 1.5	1.4 ± 1.8	Δ = -0.1; 95% CI <0.4 t = -5.9; p < 0.0001

ITT, intention-to-treat analysis; PP, per-protocol analysis; CI, confidence interval.

^a Results are presented as the mean ± standard deviation.^b The Statistics column shows the results of the Student *t*-test modified for comparability (non-inferiority) testing. Δ is the mean difference between group 1 (Ergoferon) and group 2 (oseltamivir). The *p*-value stands for type I error.**Table 6**
Duration of fever and time to treatment-associated resolution of influenza symptoms^a

Symptom	Duration of symptoms, days					
	ITT analysis			PP analysis		
	Group 1 (n=78)	Group 2 (n=78)	Statistics ^b	Group 1 (n=75)	Group 2 (n=72)	Statistics ^b
Fever	2.1 ± 1.5	2.3 ± 1.6	Δ = -0.13; 95% CI <0.28 t = -2.4; p = 0.01	2.1 ± 1.4	2.3 ± 1.6	Δ = -0.24; 95% CI <0.17 t = -2.8; p = 0.002
Flu-related non-specific symptoms	2.7 ± 2.2	2.4 ± 2.1	Δ = 0.29; 95% CI <0.47 t = -1.7; p = 0.04	2.6 ± 2.2	2.4 ± 2.1	Δ = 0.26; 95% CI <0.44 t = -1.96; p = 0.025
Respiratory symptoms	2.8 ± 2.5	2.6 ± 2.6	Δ = 0.15; 95% CI <0.45 t = -2.1; p = 0.02	2.7 ± 2.5	2.6 ± 2.6	Δ = 0.09; 95% CI <0.40 t = -2.3; p = 0.01
All influenza symptoms	2.7 ± 2.3	2.5 ± 2.2	Δ = 0.22; 95% CI <0.37 t = -3.0; p = 0.001	2.6 ± 2.3	2.5 ± 2.2	Δ = 0.17; 95% CI <0.33 t = -3.4; p = 0.0003

ITT, intention-to-treat analysis; PP, per-protocol analysis; CI, confidence interval.

^a Results are presented as the mean ± standard deviation.^b The Statistics column shows the results of the Student *t*-test modified for comparability (non-inferiority) testing. Δ is the mean difference between group 1 (Ergoferon) and group 2 (oseltamivir). The *t*-test was calculated for differences between means to determine their significance as compared to the pre-defined delta (margin). The *p*-value stands for type I error.**Table 7**
Number of antipyretic and NSAIDs taken^a

Day	ITT analysis			PP analysis		
	Group 1 (n=78)	Group 2 (n=78)	Statistics ^b	Group 1 (n=75)	Group 2 (n=72)	Statistics ^b
1	0.65 ± 0.48	0.69 ± 0.46	Δ = -0.04; 95% CI <0.09 t = -3.16; p = 0.001	0.65 ± 0.48	0.72 ± 0.45	Δ = -0.07; 95% CI <0.06 t = -3.5; p = 0.0003
2	0.40 ± 0.49	0.49 ± 0.50	Δ = -0.09; 95% CI <0.04 t = -3.63; p = 0.0002	0.40 ± 0.49	0.49 ± 0.50	Δ = -0.09; 95% CI <0.05 t = -3.48; p = 0.0003
3	0.19 ± 0.40	0.15 ± 0.36	Δ = 0.04; 95% CI <0.14 t = -2.65; p = 0.0044	0.19 ± 0.39	0.15 ± 0.36	Δ = 0.03; 95% CI <0.14 t = -2.66; p = 0.0043
4	0.01 ± 0.11	0.04 ± 0.19	Δ = -0.03; 95% CI <0.02 t = -8.89; p < 0.0001	0.01 ± 0.12	0.04 ± 0.20	Δ = -0.03; 95% CI <0.02 t = -8.48; p < 0.0001
5	0.01 ± 0.11	0.03 ± 0.16	Δ = -0.01; 95% CI <0.02 t = -9.63; p < 0.0001	0.01 ± 0.12	0.03 ± 0.17	Δ = -0.01; 95% CI <0.02 t = -9.14; p < 0.0001

NSAID, non-steroidal anti-inflammatory drug; ITT, intention-to-treat analysis; PP, per-protocol analysis; CI, confidence interval.

^a Results are presented as the mean ± standard deviation.^b The Statistics column shows the results of the Student *t*-test modified for comparability (non-inferiority) testing. Δ is the mean difference between group 1 (Ergoferon) and group 2 (oseltamivir). The *p*-value stands for type I error.

symptoms was attained by study patients at 2.8 ± 2.5 and 2.6 ± 2.6 days, respectively (Table 6). The mean duration of all influenza symptoms was 2.7 ± 2.3 and 2.5 ± 2.2 days in group 1 and group 2, respectively. The statistical analysis of ITT and PP sets indicated consistent comparability of treatment outcomes in the two groups (Table 6). On average, most influenza symptoms had resolved after approximately 3 days of treatment, without significant differences in either ITT or PP data between the groups (Table 6).

The mean rate of antipyretic/NSAID intake on day 1 as calculated on a per-patient basis was 0.65 ± 0.48 (0.65 ± 0.48) in group 1 and 0.69 ± 0.46 (0.72 ± 0.45) in group 2 (Table 7). By day 3, this variable was reduced to 0.19 ± 0.40 (0.19 ± 0.39) in group 1 and

0.15 ± 0.36 (0.15 ± 0.36) in group 2. The statistical analysis demonstrated consistent comparability of endpoint values in the treatment groups (*p* < 0.005 (*p* < 0.005)).

By day 7, the mean EQ5D score in group 1 was 5.4 ± 0.8 (versus a baseline score of 9.4 ± 1.9), indicating a significant improvement in patient health (Δ₁₋₇ = -4.0), and similar results were obtained in group 2 (5.5 ± 0.9 and 9.2 ± 2.3, respectively; Δ₁₋₇ = -3.7) (Table 8).

Based on patient self-reported health estimates on the health-rating scale, the mean total score in group 1 was increased more than two-fold, from 42.1 ± 18.4 at baseline to 87.7 ± 10.6 (Δ₁₋₇ = 45.6), and an increase from 46.7 ± 15.1 to 87.8 ± 11.4 (Δ₁₋₇ = 41.1) was observed in group 2. These data were consistent

Table 8
Total EQ5D scores and self-reported health estimates^a

Day	ITT analysis			PP analysis		
	Group 1 (n = 78)	Group 2 (n = 78)	Statistics ^b	Group 1 (n = 75)	Group 2 (n = 72)	Statistics ^b
EQ5D Questionnaire, score						
1	9.4 ± 1.9	9.2 ± 2.3		9.6 ± 1.9	9.4 ± 2.2	
7	5.4 ± 0.8	5.5 ± 0.9		5.3 ± 0.9	5.4 ± 0.8	
Δ1–7	−4.1 ± 1.8	−3.7 ± 2.3	Δ = −0.4; 95% CI <0.2 t = −3.4; p = 0.0005	−4.2 ± 1.8	−3.9 ± 2.2	Δ = −0.3; 95% CI <0.3 t = −3.2; p = 0.0009
Health rating scale, score						
1	42.1 ± 18.4	46.7 ± 15.1		41.6 ± 18.2	46.2 ± 15.4	
7	87.7 ± 10.6	87.8 ± 11.4		87.7 ± 10.7	88.0 ± 10.6	
Δ1–7	45.5 ± 20.3	41.2 ± 16.4	Δ = 4.5; 95% CI >−0.5 t = 4.3; p < 0.0001	46.1 ± 20.0	41.8 ± 15.7	Δ = 4.2; 95% CI >−0.7 t = 4.3; p < 0.0001

EQ5D, European Quality of Life Questionnaire; ITT, intention-to-treat analysis; PP, per-protocol analysis; Δ1–7, within-group mean difference on days 1 and 7; CI, confidence interval.

^a Results are presented as the mean ± standard deviation.

^b The Statistics column shows the results of the Student *t*-test modified for comparability (non-inferiority) testing. Δ is the between-group difference in Δ1–7 values. The *p*-value stands for type I error.

Table 9
Number of patients with complications requiring antibacterial therapy

ITT analysis			PP analysis		
Group 1 (n = 78)	Group 2 (n = 78)	Statistics ^a	Group 1 (n = 75)	Group 2 (n = 72)	Statistics ^a
0	2 (3%)	Δ = −3% (−7% to 2%) Z = 11.9; p < 0.0001	0	1 (1%)	Δ = −1% (−5% to 3%) Z = 14.5; p < 0.0001

ITT, intention-to-treat analysis; PP, per-protocol analysis.

^a The Statistics column shows the results of the frequency analysis for comparability testing (non-inferiority Wald test) with 95% confidence intervals in parentheses.

with the PP analysis (Table 8). Statistical analysis of variations in total EQ5D score and in patient self-reported health estimates confirmed significant between-group comparability (Table 8).

In group 1, neither worsening of illness nor complications requiring antibacterial therapy or hospitalization were recorded, whereas two patients in group 2 developed complications (one case of community-acquired pneumonia affecting the lower lobe of the left lung on day 4, and one case of acute maxillary sinusitis on day 5) and were prescribed antibiotic therapy (Table 9).

3.4. Safety analysis

A total of 25 AEs were reported for 11 subjects in group 1, and 24 AEs were reported for 15 subjects in group 2. No serious AEs were recorded. The incidence of AEs did not differ between the groups (Table 10). The total list of AEs in the safety population is presented in the [Supplementary Material](#) (Table S3).

In group 1, all AEs were mild with an uncertain (*n* = 22) or possible (*n* = 3) relationship to the study treatment as determined by the physician. Most patients who experienced AEs (*n* = 10) had some abnormal laboratory findings, as revealed by the examination on day 7. The total number of abnormal laboratory findings in group 1 was 23, and all of them were mild.

Table 10
Number of patients with AEs and number of AEs per patient

Variable	Group 1 (n = 81)	Group 2 (n = 80)	Statistics ^a
Number of patients with AEs, <i>n</i> (%)	11 (14%)	15 (19%)	Δ = −5% (−18% to 7%) Z = 4.1; p < 0.0001
Number of AEs in group	25	24	NA
Number of AEs per patient	0.30 ± 1.07	0.28 ± 0.73	Δ = 0.02; 95% CI <0.26 t = −0.2; p = 0.405

AE, adverse event; NA, not applicable; CI, confidence interval.

^a For the number of patients with AEs, the Statistics column shows the results of the frequency analysis (non-inferiority Wald test) with 95% confidence intervals in parentheses. For the number of AEs per patient, the Statistics column shows the results of the Student *t*-test modified for comparability (non-inferiority) testing.

In group 2, a total of five moderate and 19 mild AE cases were reported, including acute pneumonia (*n* = 1), acute maxillary sinusitis (*n* = 1), difficulty breathing (*n* = 1), depressed mood disorder (*n* = 1), and nausea (*n* = 2). The total number of abnormal laboratory findings on day 7 in group 2 was 18. Five AEs were unrelated to the treatment; 19 AEs had an uncertain (*n* = 17) or possible (*n* = 2) relationship to the treatment.

Neither Ergoferon nor oseltamivir had negative effects on vital functions (see [Supplementary Material](#), Table S4).

There was no evidence of any drug–drug interaction with medications administered concomitantly with Ergoferon or oseltamivir (see [Supplementary Material](#), Table S2).

Patients in both groups had approximately 100% compliance with the therapies (Table 11). Patients in group 1 had good tolerance of Ergoferon and all recovered at the end of treatment. In group 2, two patients had complications requiring antibacterial treatment.

4. Discussion

Oseltamivir has been evaluated extensively in randomized controlled trials^{7,8,20} and was chosen as the comparator to demonstrate the non-inferiority of Ergoferon in patients with

Table 11
Rates of compliance with the study therapies^a

Variable	ITT analysis			PP analysis		
	Group 1 (n = 78)	Group 2 (n = 78)	Statistics ^b	Group 1 (n = 75)	Group 2 (n = 72)	Statistics ^b
Compliance, %	101 ± 4	100 ± 0	Δ = -1; 95% CI > -2 t = 18.1; p < 0.0001	101 ± 4	100 ± 0	Δ = -1; 95% CI > -2 t = 19.0; p < 0.0001

ITT, intention-to-treat analysis; PP, per-protocol analysis; CI, confidence interval.

^a Results are presented as the mean ± standard deviation.

^b The Statistics column shows the results of Student *t*-test modified for comparability (non-inferiority) testing. Δ is the mean difference between group 1 (Ergoferon) and group 2 (oseltamivir). The *p*-value stands for type I error.

seasonal influenza. At the same time, it should be mentioned that in spite of the fact that the efficacy of oseltamivir has been questioned (Cochrane systematic review, 2014),²¹ the World Health Organization (WHO) recommends it as the first-line influenza treatment (<http://www.who.int/mediacentre/factsheets/fs211/en/>) and the drug is on the WHO List of Essential Medicines.²²

The final results of this study support those of the previously published interim analysis in which only about a third of the final number of patients was enrolled.¹⁹ The therapeutic effect of Ergoferon is comparable to that of oseltamivir. The percentage of patients with absence of fever, which is known to correlate with virus clearance and the antiviral efficacy of the therapy,²³ was evaluated as the primary efficacy endpoint. Ergoferon was shown to have the same effect as oseltamivir on the duration of fever: over two-thirds of patients reported a body temperature of ≤37.0 °C by the end of day 4. At treatment completion, the percentages of patients with normal morning and evening body temperatures were similar in the two groups. The mean duration of the febrile period in the Ergoferon group was approximately 2 days without significant difference from the oseltamivir group, and this efficacy is similar to the previously published data.

Ergoferon intake halved the severity of the influenza symptoms (headache, muscular pain, and joint pain) by day 3. On average, the mean duration of influenza symptoms was about 2 days in the Ergoferon group and was comparable to that in the oseltamivir group. A meta-analysis published in *The Lancet* demonstrated a median time to influenza symptom alleviation of 97.5 h (or 4.1 days) for ambulant patients receiving oseltamivir.²⁴ In addition, the statistical analysis indicated consistent comparability of the rates of antipyretic use in both groups.

Furthermore, there were no cases of worsening illness or complications among the study patients. Improved quality of life estimates reported by the patients taking Ergoferon were consistent with the significant improvement in total EQ5D scores and patient health self-assessments from baseline.

The pharmacological activity of Ergoferon is ensured by the combined action of its components on the antiviral immune response and virus-induced respiratory tract inflammation. Each component of Ergoferon exerts a modulating effect on its respective target, as is a common feature of released-active forms of antibodies.¹⁰ The main component of the drug – technologically treated forms of antibodies to IFN-γ – increases the expression of IFN-γ (a key cytokine participating in the antiviral immune response), IFN-α/β, and associated interleukins (IL-2, IL-4, IL-10). It also improves the ligand–receptor interaction of IFN-γ with its receptor, normalizes the concentration and functional activity of natural antibodies to IFN-γ, induces antigen expression of major histocompatibility complex (MHC I and MHC II) and Fc-receptors, stimulates natural killer (NK) cell and monocyte functional activity, and activates a mixed Th1 and Th2 immune response.^{16,25} Other components of the drug, technologically treated forms of antibodies to histamine and to CD4, have effects on histamine receptor²⁶ and CD4 receptor,²⁷ respectively.

This study has some limitations that could be considered as sources of bias: the open-label trial design, the absence of a placebo group and an untreated group, the long enrollment period (such that the outcome of many patients was known before others had been enrolled), a number of measurements of key variables performed, and the use of patient self-report.

In conclusion, Ergoferon and oseltamivir were equally effective and safe in the treatment of adults with seasonal influenza. It is hoped that Ergoferon will become useful in the treatment of patients infected with virus that has developed resistance to current influenza drugs. The cost of a 5-day treatment with Ergoferon is significantly lower than that of a 5-day treatment with Tamiflu.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ijid.2016.09.002>

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