



# Efficacy and Safety of Aviron Rapid® in 18-60-year-old Patients with Clinical Diagnosis of Acute Respiratory Viral Infection: a Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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## Abstract

**Aim:** Prevention and treatment of upper respiratory tract infections are given the highest priority because of the tremendous health and economic impact of these diseases. Development of novel effective and safe options for treatment can contribute considerably to decrease the burden of disease.

**Materials and methods:** We designed a multicenter, randomized, double-blind, placebo-controlled study in ambulatory-treated adult patients with a clinical diagnosis of acute upper respiratory tract viral infection. The patients (18-60 years old) were randomized into two groups and followed-up for 5 days. Group 1 received the standard symptomatic therapy + Aviron Rapid®, and Group 2 received the standard symptomatic therapy + placebo. The primary endpoint of the study was defined as the duration of disease measured by the percentages of disease-free patients for every 12-hour period of the study.

**Results:** Treating clinically relevant patients with the natural product Aviron Rapid® for 5 days decreases the duration of disease, the intake of antipyretics and the severity of symptoms. Significant difference between the tested groups for most of studied parameters was found as soon as 12 or 24 hours after initiation of administration in favour of active arm and was the most prominent on days 3 and 4. Significant decrease in the total score of symptoms severity was achieved on day 4 and extended to the end of study. There were no differences in the adverse events between the groups and the tested product demonstrated excellent safety profile.

**Conclusions:** This study is a clinical confirmation of well documented antiviral activity of the product targeting multiple points in viral replication and covering broad spectrum viral pathogens.

## Keywords

antiviral, Aviron Rapid®, treatment, upper respiratory tract infection

## INTRODUCTION

Acute upper respiratory tract infections (URTIs) are the most common infectious pathology in routine clinical practice. The high incidence, between 2-5 episodes and 7-10 episodes per year in adults and in school-age children, respectively, can be explained by the easy airdrops transmission, relatively short incubation period and short-lasting specific immunity after acute illness.<sup>1</sup> Acute URTIs are the most common reason for physician office visits; they have tremendous impact on quality of life representing significant amount of direct and indirect healthcare costs. Therefore, prevention and control of URTIs are the main clinical targets with significant health and economic impact.<sup>2</sup> Virus etiology of URTIs is reported to be between 40% and 90% globally and more than 80% of URTIs in children are related to different viruses.<sup>3</sup> To date, more than 200 viruses have been identified as causative agents for URTIs. They can be mainly grouped in one-family DNA viruses (*Adenoviridae*), and four-families RNA viruses (*Orthomyxoviridae*, *Paramyxoviridae*, *Picornaviridae* u *Coronaviridae*).<sup>2</sup> In the daily clinical practice, diagnosis is usually empirical and based on clinical signs. Lack of information about the disease etiology and lack of specific treatment for most of viral pathogens, necessitate nonspecific, most commonly symptomatic treatment only.<sup>4</sup>

Symptoms relief is the main aim of empiric URTIs treatment. Despite the many symptomatic remedies providing temporary relief of symptoms, there is no available evidence that they shorten time for symptom alleviation.<sup>5</sup> Antibiotics are not effective against viral pathogens and are not recommended for prevention of secondary bacterial infections in immunocompromised patients.<sup>6</sup> Another approach to managing the URTIs is the usage of immunomodulators. Some of them stimulate interferons secretion, others, like inosine acedoben dimepranol, have positive effect on different immune responses *in vitro* and *in vivo*. Still the available data of its effectiveness for prevention and treatment of URTIs are inconclusive and inconsistent.<sup>7-9</sup>

Despite of the revolutionary progress of medical science, the treatment of viral URTIs remains a significant challenge. Very few antiviral drugs have been established as a routine URTIs approach in daily outpatient clinical practice.<sup>2,10</sup> Those are the M2 channel blockers (amantadine and rimantadine) that demonstrated effectiveness against influenza A virus only, and neuraminidase inhibitors (oseltamivir and zanamivir), with activity against influenza A and B viruses.<sup>11</sup> Another challenge for viral URTIs treatment is the lack of proven effect against flu-like illness, defined as presence of two or more symptoms, including nasal congestion, headache, chills/sweating, sore throat, cough, fatigue, myalgia, and fever.<sup>12</sup> Frequent mutations of influenza virus has also led to considerable resistance to M2 channel blockers making their effectiveness questionable.<sup>13</sup> All those challenges clearly defined the need of new therapeutic options for treatment of viral URTIs, including alternative ones, with potential broad spectrum antiviral

efficacy against pathogens responsible for most common URTIs and real implications for clinical practice.

## AIM

The aim of current clinical trial is to evaluate the effect of Aviron Rapid®, registered as food supplement in adult patients with clinical diagnosis of viral URTI and treated according to usual clinical practice. Aviron Rapid® is a combination of three well studied and clinically tested active ingredients: proprietary humic acid racemic mixture, proprietary spirulina extract, and andrographolide.

## MATERIALS AND METHODS

### Treatment options

Group 1 - Aviron Rapid®. Every 647 mg tablet contains 10 mg andrographolide, 100 mg proprietary extract from spirulina and 250 mg proprietary humic acid racemic mixture. Group 2 - placebo available as exactly the same 647 mg white tablets in same package as Group 1.

Every package had a unique number generated by randomization software. Dosage of investigated product and placebo was as specified by manufacturer. Day 1: 3 times × 3 tablets; day 2: 3 times × 2 tablets; day 3 to day 5: 3 times × 1 tablet/daily.

### Study review

A multicenter, randomized, double-blind, placebo-controlled study was performed in 85 outpatient centres. Informed consent was obtained in all cases. The study was conducted according to the Declaration of Helsinki. First patient was enrolled on 27.01.2020 and last patient was completed on 09.03.2020. Two clinical assessments were made by participating physicians – on day 1 (initiation) and day 6 (closing visit). From the evening of day 1 to the morning of day 6 the patients assessed their symptoms in a diary at every 12 hours.

### Selection of patients

Patients were enrolled in the study based on inclusion and exclusion criteria. Inclusion criteria: 18-60 years old ambulatory-treated patients with a clinical diagnosis of acute upper respiratory tract viral infection with: axillary temperature >37°C and one or more of the following symptoms: nasal congestion, cough, sore throat, headache, fatigue, and sleep disturbances. The symptoms should be present no more than 24 hours before examination. Exclusion criteria: treatment with inosine acedoben dimepranol, rimantadine hydrochloride, neuraminidase inhibitors - oseltamivir, zanamivir; suspected bacterial infection, pneumonia or other, that have to be treated with antibiotics; clinical symptoms of severe flu/acute URTI needed hospitalization; initial symptoms similar to URTI but related to different

diseases (other infectious diseases, flu-like syndrome in systemic connective tissue disease, onco-hematologic and other diseases); medical history for primary or secondary immune deficiencies; medical history of sarcoidosis; diabetes or serious chronic diseases of heart, liver, kidney or brain; cancer; exacerbation or decompensation of chronic disease affecting ability to participate in the clinical trial; medical history of allergy; allergy/intolerance to some of ingredients of the tested product; patients with malabsorption including congenital or acquired lactase or other disaccharidase deficit; patients with galactosemia; drug addicted patients; consumption of 2 or more alcohol units per day; patients with psychiatric disease; patients participating in another clinical study in the last 3 months. All patients that started antibiotic treatment during the study were also excluded from data analysis.

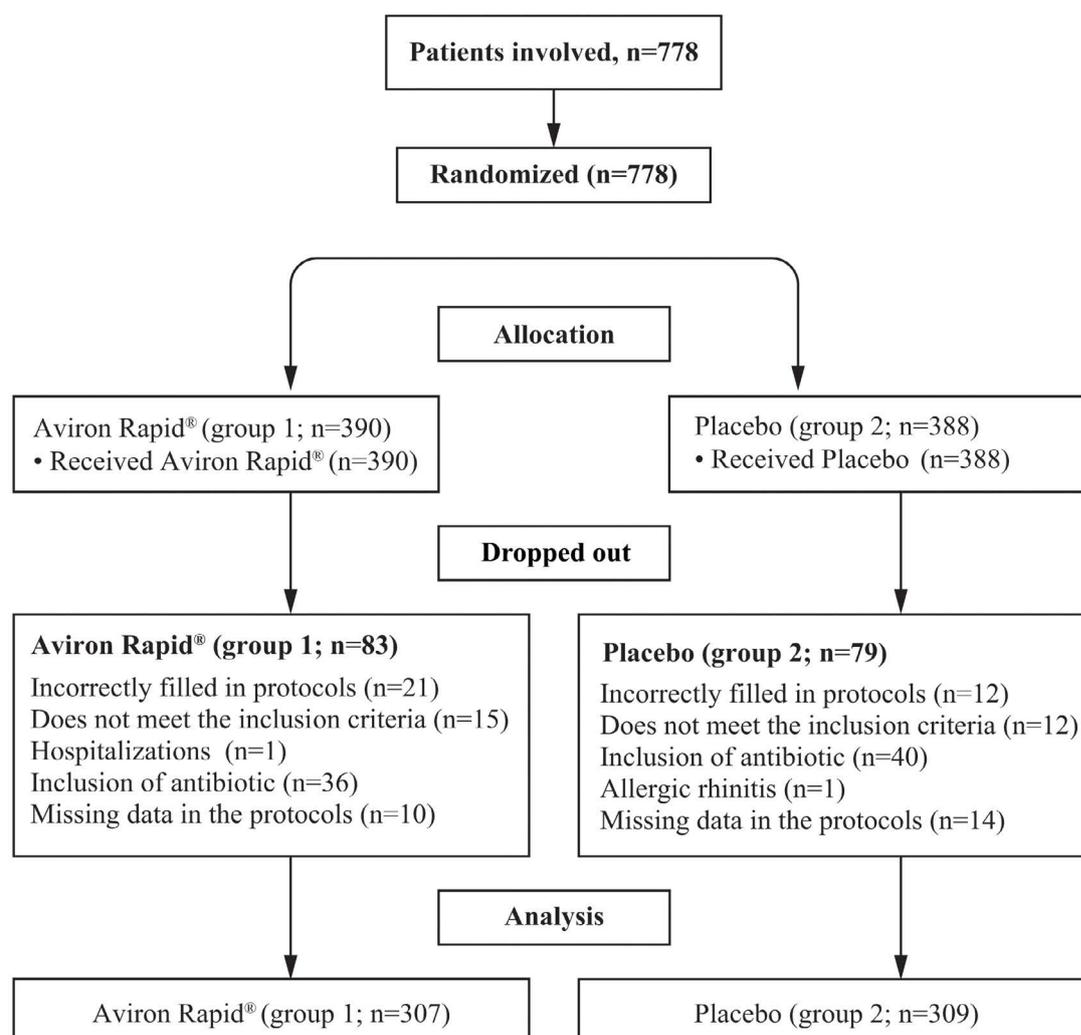
### Baseline data

A total number of 778 patients were included in the study (Group 1, n=390, and Group 2, n=388). After randomiza-

tion, 162 patients were excluded from final data analysis (Fig. 1). All demographic and clinical parameters were comparable between treated and control groups. Average age of participants was 39.27 years; females were 60.7% of the study population (Table 1). There was no significant difference between groups in mean axillary temperature and total score for severity of symptoms (Table 2).

### Patient evaluation

Clinical evaluation on day 1 included: measurement of axillary temperature, physical examination, and symptoms assessment. Severity of every symptom was evaluated by a visual analogue scale (VAS) where 0 indicates lack of symptoms, 1-2 = very mild symptoms, 3-4 = mild, 5-6 = moderate, 7-8 = severe, 9 = very severe, and 10 indicates extraordinary severe symptoms. Clinical evaluation on day 6 included: measurement of axillary temperature, physical examination, and general evaluation of patients' condition ticked as healthy or ill. If during the study, a patient became worse, a second clinical assessment was made before day 6,



**Figure 1.** Scheme of patient randomization and distribution and the experimental therapeutic design.

**Table 1.** Patient demographics

	Group 1	Group 2	Total
Total patients	390	388	778
Patients analyzed	307	309	616
Age	39.64	38.91	39.27
Female	191 (62.2%)	183 (59.2%)	374 (60.7%)
Male	116 (37.8%)	126 (40.8%)	242 (39.3%)

**Table 2.** Baseline symptoms, axillary temperature, total severity of symptoms

Initial symptoms	Group 1	Group 2	P value†
	n=307	n=309	
Total severity of symptoms	27.77	27.15	0.449
Average axillary temperature, °C	37.98	37.99	0.797
Runny nose	263 (85.7%)	255 (82.5%)	0.286
Cough	224 (73.0%)	221 (71.5%)	0.689
Sore throat	255 (83.1%)	253 (81.9%)	0.699
Headache	258 (84.0%)	266 (86.1%)	0.476
Fatigue	276 (89.9%)	286 (92.6%)	0.244
Sleep disturbance	126 (41.0%)	138 (44.7%)	0.364

† - Sig. (2-tailed) t-test for Equality of Means

and the date, the reason for examination, new treatment or hospitalization were registered in the protocol. All patients received a diary and filled the data for axillary temperature, VAS score of symptoms and non-steroid anti-inflammatory drugs (NSAIDs) intake.

### Treatment

The patients who met the study criteria were randomized by Randsamp software and were allocated to one of the following treatment groups: Group 1: standard symptomatic therapy + Aviron Rapid®, Group 2: standard symptomatic therapy + placebo. The following drugs were used as a standard symptomatic treatment: NSAIDs, decongestants, bronchodilators, mucolytics, antitussives and other drugs for treatment of chronic diseases. Use of other antiviral remedies, antihistamines, antibiotics, and interferons was not allowed. Usage of NSAIDs and other symptomatic drugs was recorded in physician protocols and patient diaries.

### Efficacy endpoints

Primary endpoint of the study was defined as duration of disease measured by the percentage of disease-free patients for every 12-hour period of the study. Disease-free patient was defined as follows: lasting improvement of every symptom to score “very mild” or “lack of symptoms” (severity  $\leq 2$  points) and the summary score of all symptoms must be  $\leq 12$  points; lasting decrease of axillary temperature to  $<37.0^{\circ}\text{C}$ . Lasting decrease was defined as a temperature  $<37.0^{\circ}\text{C}$  in two consecutive 12-hour periods measurements and not measured again  $\geq 37.0^{\circ}\text{C}$  to the end of study;

measured axillary temperature  $<37.0^{\circ}\text{C}$  must be without concomitant intake of antipyretics;

Secondary endpoints are defined as follows: percentages of patients with lasting decrease of temperature  $<37.0^{\circ}\text{C}$ ; time to lasting decrease of temperature  $<37.0^{\circ}\text{C}$ ; decrease of the number of patients taking antipyretics; time on antipyretic treatment; decrease of severity of symptoms; percentage of patients with lasting relief of every single

symptom (nasal congestion, cough, sore throat, headache, fatigue, sleep disturbances).

### Statistical analysis

This study was based on parallel group design with superiority hypothesis. For equality of means, parametric independent samples T test was used. For difference of relative parts of two samples in one-side critical area a Z-test was used. A one-tailed probability value  $p \leq 0.05$  was considered statistically significant. All statistical evaluations were done using SPSS 17 and STATA 10.1.

### Safety analysis

Safety was evaluated in all patients completed the study in both treated and control groups, included in data analysis, and received at least one dose of Aviron Rapid® (n=307) or placebo (n=309). All registered adverse events (AE) and results of physical examination are summarized in a table by treatment group.

## RESULTS

### Primary endpoint

Statistically significant difference was found 24 hours after initiation of treatment in the relative number of disease-free patients in favour of Group 1 ( $p < 0.01$ ). On day 3, significantly more patients in Group 1 (20.5%, n=97)

were disease-free vs. patients receiving placebo (8.4%, n=56) ( $p<0.01$ ). The difference between treatment groups remained significant to the end of study in favour of Group 1 (91.2%, n=280) vs. Group 2 (82.8%, n=256) ( $p<0.01$ ) (Fig. 2). Average time of disease in Group 1 was 77 hours, vs. 87 hours in Group 2 ( $p<0.001$ ).

## Secondary endpoints

### Lasting decrease of temperature

Patients in Group 1 demonstrated significantly faster and lasting decrease of axillary temperature below 37.0°C ( $p<0.001$ ). As soon as 24 hours after beginning of treatment, significantly more patients in Group 1 ( $p<0.001$ ) had temperature <37.0°C compared to Group 2 and this difference remained significant for all measured points of the study. On day three, 73% more patients in Group 1 (47.9%, n=147) had temperature <37.0°C measured in 2 consecutive 12-hour periods vs Group 2 – 27.5% (n=85) ( $p<0.001$ ). Average time of patients with fever was 66 hours in Group 1 vs. 79 hours in Group 2 ( $p<0.001$ ) (Fig. 3).

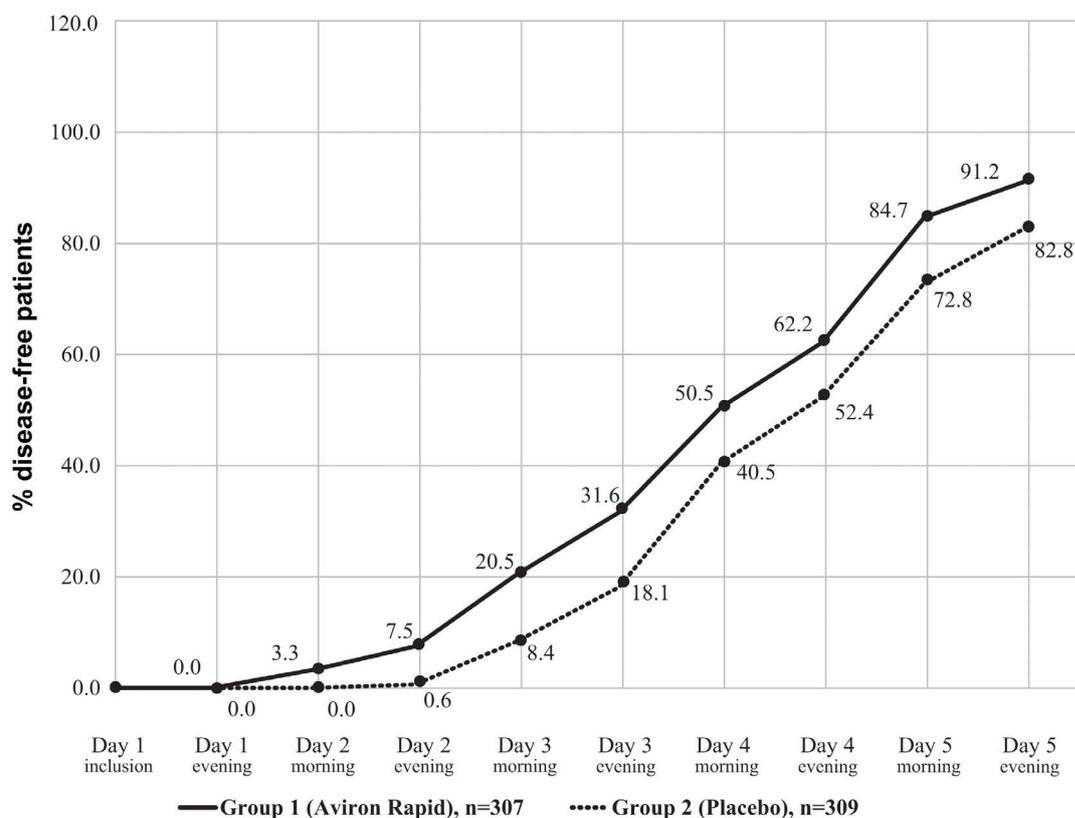
### Decrease the number of patients taking antipyretics

Significantly lower number of patients taking antipyretics

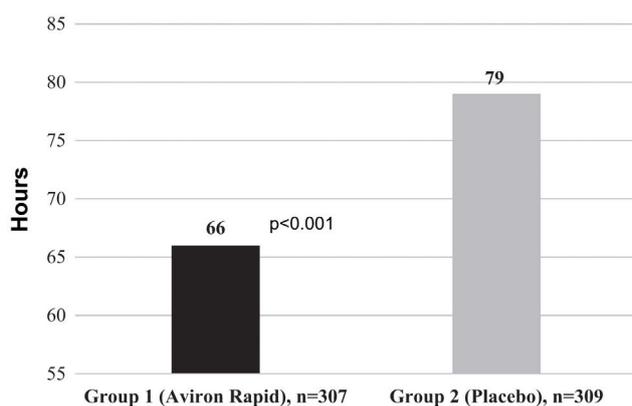
were found in Group 1 compared to Group 2, reaching significance 12 hours after initiation of treatment ( $p<0.05$ ). The difference remained significant through all periods of study, with maximal value on day 3 – Group 1, 14.3% (n=44) vs. Group 2, 58.6% (n=181) ( $p<0.001$ ). Average time of antipyretics intake was also significantly lower in Group 1 – 44 hours vs. 68 hours in Group 2 ( $p<0.001$ ) (Fig. 4).

### Decrease of symptoms severity

The total score of all evaluated symptoms reached statistical significance in favour of Group 1 vs. Group 2 starting from day 4 ( $p<0.021$ ). The significance of observed benefit in Group 1 remained unchanged till the end of study ( $p<0.001$ ) on day 5 (Table 3). The same trend was observed for the VAS score of every individual score for 3 of symptoms, included as secondary endpoint – nasal congestion, cough, and sore throat. However, starting from day 4, significant difference ( $p<0.0027$ ) was observed in all remaining periods to the end of study only for the sore throat symptom. At the end of study 3.8% of patients in Group 1 (n=11) reported sore throat symptom vs. 7.5% in Group 2 (n=23) ( $p<0.0267$ ). Statistically significant differences were not observed between the study groups for the other 3 individual symptoms included in the assessment (headache, fatigue, and sleep disturbances).



**Figure 2.** Percentage of disease-free patients at every 12-hours period in studied groups. Solid line represents patients in group 1, dotted line – patients in group 2. Significant difference was reached 24 hours after inclusion ( $p<0.01$ ), and present for every period to the end of study ( $p<0.01$  at last observed period).



**Figure 3.** Average duration of fever in hours (66 in group 1 vs 79 in group 2,  $p<0.001$ ), measured by time to lasting (sustainable for more than two consecutive 12-hours periods and lasting to the end of study), decrease of temperature  $<37.0^{\circ}\text{C}$ .

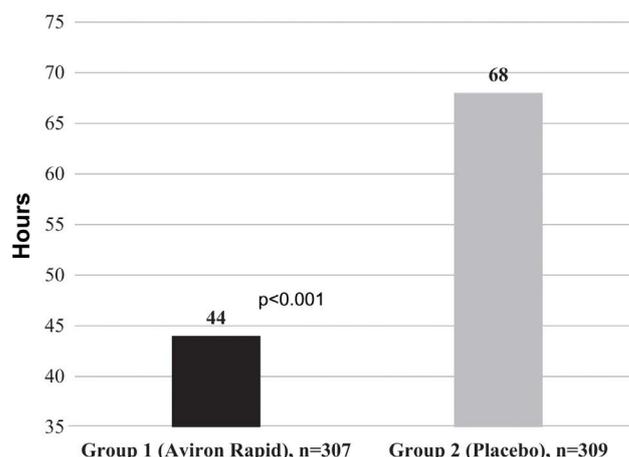
**Table 3.** Symptom severity at every period

Time period	Group 1 n=307	Group 2 n=309	p-Value†
Day 1 inclusion	27.77	27.15	0.449
Day 1 - evening	28.66	29.03	0.673
Day 2 - morning	24.70	25.81	0.213
Day 2 - evening	21.05	22.20	0.190
Day 3 - morning	15.91	17.05	0.144
Day 3 - evening	13.16	14.54	0.057
Day 4 - morning	9.39	10.76	0.021
Day 4 - evening	7.15	8.84	0.002
Day 5 - morning	4.74	6.23	0.001
Day 5 - evening	3.14	4.73	$<0.001$

† - Sig. (2-tailed) t-test for Equality of Means

**Table 4.** Adverse events reported

SERIOUS ADVERSE EVENTS				
	Group 1 (n=390)		Group 2 (n=388)	
	Reported (n)	Reported (%)	Reported (%)	Reported (n)
Serious adverse events reported	0	0%	0	0%
ANY ADVERSE EVENTS				
	Group 1 (n=390)		Group 2 (n=388)	
	Reported (n)	Reported (%)	Reported (n)	Reported (%)
Allergic reaction	0	0.00%	1	0.30%
Hospitalization	1	0.30%	0	0.00%
Shingles	2	0.50%	2	0.50%
Antibiotic treatment unknown reason	33	7.90%	34	8.20%
Bronchitis	3	0.80%	1	0.30%
Laryngitis	0	0.00%	1	0.30%
Acute tonsillitis	0	0.00%	1	0.30%
Sinusitis	0	0.00%	3	0.80%
<b>TOTAL ADVERSE EVENTS</b>	<b>39</b>	<b>10.00%</b>	<b>43</b>	<b>11.08%</b>



**Figure 4.** Average duration of antipyretics intake (44 in group 1 vs 68 in group 2,  $p<0.001$ ), measured by time to lasting (sustainable for more than two consecutive 12-hours periods and lasting to the end of study), antipyretics-free periods.

### Tolerance and safety assessment

No allergic reactions or allergy exacerbations was reported in the Group 1 vs one reported in the placebo group. No drug interaction was observed in both groups in concomitant use of standard care – NSAIDs, decongestants, bronchodilators, mucolytics, and drugs used for treatment of chronic diseases. One patient from Group 1 was hospitalized (Table 4). In the current study, Aviron Rapid® demonstrated excellent safety profile comparable with placebo group and lack of drug interactions.

## DISCUSSION

Prevention and treatment of URTIs are among the most important targets for scientists because of their tremendous impact on society. URTIs are significant burden for healthcare and economy for each country. Despite the tremendous efforts of army of scientists and huge amounts of allocated resources, there are several challenges keeping progress slow and unsatisfactory. The main challenge is that most of URTIs are caused by viruses – a very tough therapeutic target.<sup>3</sup> Up to date very few antiviral agents are available for routine use in daily outpatient clinical practice – neuraminidase inhibitors and M2 channel blockers. The problem is that they have demonstrated an effect only against influenza virus – a small portion of more than 200 viral pathogens causing URTIs.<sup>2,12</sup>

Our study addresses some of the issues by different, alternative approach based on a natural therapeutic product, supported by relevant scientific data. The targets are the most common URTIs with unknown etiology treated routinely in outpatient GP practice. Some reports suggest the broad spectrum antiviral activity of active ingredients *in vitro* and *in vivo* against common viral pathogens: Influenza A<sup>14-16</sup>, Influenza B<sup>14</sup>, Coxsackie A9<sup>17</sup>, Coxsackievirus A<sup>16</sup>, Coxsackievirus B<sup>4,14</sup>, Adenovirus type 7<sup>18</sup>, RSV<sup>19</sup>, CMV<sup>14,17</sup>, EBV<sup>20</sup>, HSV 1<sup>21-22</sup>, HSV-2<sup>14</sup>, Astrovirus 1, Rotavirus Wa, and Adenovirus 40<sup>18</sup>. This combination has potential synergic effect and targets different stages of virus replication in host cells: inhibits attachment of the virus to the cell surface<sup>17</sup>; suppresses fusion of virus envelope with endosomal membrane by structural change of tripeptide sequence Phe-Leu-Gly on virus envelope glycoproteins<sup>19</sup>; inhibits endonuclease activity of viral RNA-polymerase<sup>15</sup> and intracellular transportation of viral particles<sup>23</sup>. Published data from randomized clinical trials and systematic reviews demonstrates promising evidence for efficacy of active ingredients in patients with flu, common cold and URTIs.<sup>24-27</sup> The study we performed is a step further to test hypothesis that potential synergy of active ingredients can be transformed into clinical benefits, tested by multicenter, randomized, double-blind, placebo-controlled study. Performed in real clinical outpatient practice, the study met its primary endpoint for efficacy and almost all secondary endpoints. The most interesting results are early split of curves and achieving statistical significance as early as 24 hours for disease-free patients and stable fever alleviation for patients taking less NSAIDs in active group. This difference remained sustainable during the study period and reached biggest difference on day 3, once again confirming the fast action of studied product on disease progression. Symptoms relief had not so prominent difference, but the trends were similar resulting in statistically significant difference for total symptom score and sore throat relief. This may be due to different factors and we suppose that patients in placebo group used more NSAIDs and other symptomatic therapies that could diminish severity of some symptoms. This intriguing study is a promising step forward in

chasing for effective and safe solution for etiologic treatment of acute URTIs. More studies needed to test effectiveness of Aviron Rapid® in different age groups and with specific viral pathogens to confirm those promising results.

## CONCLUSIONS

This study is the first clinical evidence that alternative approach with the natural product Aviron Rapid® can be effective in treatment of adult patients with clinical diagnosis of acute respiratory viral infection. Our study demonstrated that the early start of the product intake on the top of standard symptomatic therapy can decrease the number of ill patients and patients with fever by 73% on day 3 compared to placebo group ( $p < 0.01$  and  $p < 0.001$ , for relative numbers, respectively) and can significantly decrease the number of patients taking NSAIDs. For example, on day 3, four times fewer patients in the Aviron group ( $n=44$ ) used antipyretics vs. placebo ( $n=181$ ) ( $p < 0.001$  for relative numbers). This study is a clinical confirmation of well documented antiviral product activity targeting multiple points in viral replication and covering broad spectrum viral pathogens.

## Acknowledgements

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# Эффективность и безопасность Aviron Rapid® у пациентов в возрасте 18–60 лет с клиническим диагнозом острой респираторной вирусной инфекции: многоцентровое рандомизированное двойное слепое плацебо-контролируемое клиническое исследование

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## Резюме

**Цель:** Профилактика и лечение инфекций верхних дыхательных путей имеют наивысший приоритет из-за огромного воздействия этих заболеваний на здоровье и экономику. Разработка новых эффективных и безопасных вариантов лечения может существенно снизить бремя болезни.

**Материалы и методы:** Мы провели многоцентровое рандомизированное двойное слепое плацебо-контролируемое исследование с участием взрослых пациентов, находящихся на амбулаторном лечении с клиническим диагнозом острой вирусной инфекции верхних дыхательных путей. Пациенты (в возрасте от 18 до 60 лет) были случайным образом разделены на две группы и наблюдались в течение 5 дней. Группа 1 получала стандартную симптоматическую терапию плюс Aviron Rapid®, а группа 2 получала стандартную симптоматическую терапию плюс плацебо. Конечная точка исследования определялась как продолжительность заболевания, измеряемая процентом пациентов, не затронутых заболеванием, в течение каждого 12-часового периода исследования.

**Результаты:** Лечение соответствующих пациентов натуральным продуктом Aviron Rapid® в течение 5 дней уменьшило продолжительность заболевания, приём жаропонижающих средств и тяжесть симптомов. Значительная разница между исследуемыми группами по большинству изучаемых параметров была обнаружена через 12 или 24 часа после начала приёма в пользу активной группы и была наиболее выражена на 3-й и 4-й дни. Значительное снижение общей оценки тяжести симптомов была достигнута в течение 4-го дня и продолжалась до конца исследования. Не было различий между побочными эффектами между группами, и протестированный продукт показал отличный профиль безопасности.

**Заключение:** Это исследование является клиническим подтверждением хорошо задокументированной противовирусной активности продукта, который нацелен на многие моменты репликации вируса и охватывает широкий спектр вирусных патогенов.

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## Ключевые слова

противовирусный, Aviron Rapid®, лечение, инфекции верхних дыхательных путей

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