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Original Article

Efficacy and Safety of Aviron Rapid® in Adolescents and Children with Viral Acute Upper Respiratory Tract Infection: a Multi-Center, Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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Abstract

Introduction: Acute upper respiratory tract infections (AURTIs) are associated with a significant burden on society attributed to medical care and loss of productivity. Novel therapies that are able to shorten disease duration, while providing symptom relief and being well tolerated, are an unmet medical need.

Aim: The main objective of this trial was to investigate the efficacy and safety of Aviron Rapid, a dietary supplement containing andrographolide, proprietary spirulina, and humic acid, in the management of AURTIs in adolescents and children.

Materials and methods: This randomized, double-blind, placebo-controlled trial was conducted between January 2020 and March 2020 in 85 general practitioner practices in Bulgaria. Adolescents (13–17 years) and children (5–12 years) with a clinical diagnosis of AURTI were randomly assigned to receive standard symptomatic therapy + Aviron Rapid or placebo for 5 and 7 days, respectively. The primary endpoints of this trial were the number (and percentage) of clinically recovered patients and the mean disease duration.

Results: In total, 380 adolescents and 401 children were enrolled in 2 age cohorts and randomly assigned to treatment with Aviron Rapid or placebo. The percentage of patients meeting the criteria for clinical recovery was significantly higher in the Aviron Rapid group compared with the placebo group from 24 and 48 hours after initiation of treatment in adolescents and children, respectively. Aviron Rapid treatment significantly reduced the duration of disease, of fever, and of antipyretics intake in both adolescents and children. When compared to placebo, a significantly higher percentage of adolescents and children on Aviron Rapid achieved a persistent decrease in temperature of less than 37°C as soon as 24 hours after starting treatment. Overall, a low number of adverse events was reported and no major differences in the incidence of individual adverse events were observed between the two treatment groups in both cohorts.

Conclusions: This clinical trial demonstrated the efficacy of Aviron Rapid in the management of acute upper respiratory tract infections in adolescents and children. Aviron Rapid treatment rapidly increased the number of clinically recovered patients and reduced overall

disease duration and duration of symptoms, in particular fever, while being well tolerated.

Trial registration: International Standard Randomised Controlled Trial Number (ISRCTN) 12221500. Retrospectively registered on 29 March 2022. [https://doi.org/10.1186/ISRCTN12221500]

Keywords

antivirals, acute upper respiratory tract infections, andrographolide, proprietary spirulina, humic acid

List of abbreviations

AE	adverse event	**FPS-R**	modified face pain scale
AURTI	acute upper respiratory tract infection	**GP**	general practitioner
CI	confidence interval	**VAS**	visual analogue scale

INTRODUCTION

Acute upper respiratory tract infections (AURTIs) are associated with a significant burden of disease. Easy airdrop transmission, short incubation time, and short-lived specific immunity contribute to more than 17 billion incident cases worldwide in 2019, resulting in a considerable non-fatal burden as the symptoms may significantly affect quality of life and productivity.[1] Healthcare costs are estimated to exceed 40 billion dollars per year in the United States[2], with an even higher economic burden attributable to loss of productivity. Children are particularly susceptible to suffering from AURTIs[3], with an average of 6 to 8 episodes per year, compared with 2 to 4 episodes in adults[4,5]. The majority of AURTIs are caused by viruses, most commonly rhinoviruses. Most treatments focus on symptom relief, including over-the-counter analgesics, zinc, nasal decongestants, and ipratropium for cough. The few safe and effective antiviral treatments available for clinical practice are not routinely used. These include M2 channel blockers[6] (amantadine and rimantadine) with demonstrated effectiveness against influenza A virus, and neuraminidase inhibitors[7] (oseltamivir and zanamivir) with activity against influenza A and B viruses. However, considering that AURTIs are mostly self-limiting and mild in severity, the use of antivirals is limited to immunocompromised patients who are more likely to develop severe infections or complications. In addition, oseltamivir-resistant viral strains have been isolated from patients, particularly immunocompromised patients.[8] Frequent mutations of influenza viruses have also led to considerable resistance to M2 channel blockers.[9] Therefore, novel therapeutic options with broad clinical antiviral efficacy and safety are an unmet medical need in the management of AURTIs.

Aviron Rapid® is a dietary supplement consisting of andrographolide, proprietary spirulina extract, and humic acid racemic mixture[10] and is indicated in adults and children (>5 years). Andrographolide, spirulina, and humic acid have shown to be effective in the treatment of AURTIs[11-15], predominantly through the prevention of viral attachment, blocking of viral reproductive mechanisms, and stimulation of the immune system.

AIM

The main objective of this trial was to evaluate the efficacy and safety of Aviron Rapid in patients with a viral AURTI clinically diagnosed by their general practitioner (GP) and treated according to standard medical practice.

MATERIALS AND METHODS

This was a multi-center, Phase 4, randomized, double-blind, placebo-controlled clinical trial with Aviron Rapid in patients with a viral AURTI, recruited from 85 GP practices in Bulgaria between January 27 and March 9, 2020. The trial included 3 age cohorts: adults (18–60 years), adolescents (13–17 years; also referred to as 'the adolescent cohort'), and children (5–12 years; also referred to as 'the pediatric cohort'). Informed consent was obtained from all participants participating in the study. Efficacy and safety data of the adult cohort in this trial have been reported previously.[10] Here, we report efficacy and safety data from the adolescent and pediatric cohorts.

Trial population

Male and female adolescents (13–17 years, both inclusive) and children (5–12 years, both inclusive) with a clinical diagnosis of a viral AURTI were enrolled in the trial. Diagnosis by the GP was based on 1) an axillary temperature of more than 37.0°C and 2) presence of one or more of the

following symptoms with onset of the first symptom within 24 hours before screening: nasal congestion, cough, sore throat, headache, fatigue, and sleep disturbance. Patients with clinical symptoms of severe flu or AURTI requiring hospitalization, or with symptoms similar to AURTI but related to other underlying diseases (infectious diseases, flu-like syndrome in systemic connective tissue disease, onco-hematologic, and other diseases) were excluded. Other exclusion criteria focused on past or current use of medications or medical disorders that could potentially confound trial results or interfere with safe completion of the trial.

Trial design

Adolescents and children presenting to a GP practice with symptoms suggestive of viral AURTIs were clinically examined (including measurement of axillary temperature) by the GP on day 1 and, if eligible, were enrolled and randomly assigned (1:1) to receive active treatment or placebo in a double-blinded fashion. Patients in the active group (Group 1) received standard symptomatic therapy + Aviron Rapid, patients in the placebo group (Group 2) received standard symptomatic therapy + placebo.

Randomization of patients was done using software designed by an external, independent vendor and was stratified by center. The active and placebo treatments were packed in blisters and delivered to the GP practices in white paper boxes, labeled with unique treatment codes. Manufacturing, packaging, and labeling were performed by the sponsor of the trial. Patients, GPs, and the sponsor's project team were blinded to treatment group assignments throughout the trial and until database lock.

On day 1, patients or their parents were given a diary to record axillary temperature, antipyretics intake, symptom severity, and recovery status twice daily with 12-hour intervals (once in the morning, once in the evening) during the treatment period, i.e., days 1 to 5 for adolescents and days 1 to 7 for children. Adolescents recorded data in the diary under supervision of their parents. For children, data was recorded by the parents. After the end of treatment, on day 6 (adolescents) or day 8 (children), patients returned to the GP practice for a closing visit. During this visit, the GP clinically examined (including measurement of axillary temperature) the patient and verified completeness of the data recorded in the diary. In addition, on day 1, symptom severity was assessed and on day 6, a general evaluation of the patient's condition (recorded as 'healthy' or 'ill') was performed.

Trial treatment

Aviron Rapid was provided as 647-mg tablets for oral use containing 10 mg andrographolide, 100 mg proprietary spirulina extract, and 250 mg proprietary humic acid racemic mixture. Placebo was provided as tablets visually matching the Aviron Rapid tablets. Patients were treated according to the following schedule: adolescents: 3 tablets 3 times daily on day 1, 2 tablets 3 times daily on day 2, and 1 tablet 3 times daily on days 3 to 5; children: 2 tablets 3 times daily on day 1 and 1 tablet 3 times daily on days 2 to 7. Tablets were taken with water, in the morning, at noon, and in the evening. Standard symptomatic therapy included non-steroidal anti-inflammatory drugs, decongestants, bronchodilators, mucolytics, antitussives, and other drugs for treatment of chronic diseases. Use of other antiviral remedies, antihistamines, antibiotics, and interferons was not allowed.

Efficacy outcome measures and assessments

The primary endpoints of this trial were the number (and percentage) of clinically recovered patients and the mean disease duration. Patients were considered clinically recovered if the following 3 criteria were met: 1) persistent improvement of every symptom to "very mild" or "lack of symptoms" (severity score <2 as measured on a visual analogue scale [VAS] for adolescents or a modified face pain scale [FPS-R] for children) until the end of follow-up and a total severity score for all symptoms [i.e. the sum of the 6 individual symptom severity scores] <12 points; 2) persistent decrease of the axillary temperature to <37.0°C, i.e. temperature <37.0°C at 2 consecutive measurements with a 12-hour interval and no new increase >37°C (i.e., fever) until the end of follow-up; 3) the decrease in axillary temperature <37°C was achieved without the use of antipyretics. The severity of the symptoms nasal congestion, cough, sore throat, headache, fatigue, and sleep disturbance was measured using a VAS (for adolescents) or FPS-R (for children) ranging from 0 to 10 with 0 = lack of symptoms and 10 = very severe symptoms. Disease duration was defined as the interval between treatment initiation and the time point at which the patient met the criteria for clinically recovery. The primary endpoints were assessed twice daily with 12-hour intervals during the treatment period (days 1 to 5 for adolescents or days 1 to 7 for children) and recorded in the patient's diary.

Secondary efficacy endpoints included number (and percentage) of patients with persistent decrease of the axillary temperature <37.0°C without the use of antipyretics, mean time to persistent decrease of the axillary temperature <37.0°C, number (and percentage) of patients taking antipyretics, mean duration of antipyretic treatment, mean total severity score for all symptoms, number (and percentage) of patients with persistent improvement of a particular symptom (severity score <2), and number (and percentage) of patients considered fully recovered. Patients were considered fully recovered if at 2 consecutive measurements with a 12-hour interval they scored 2 or 3 on a scale ranging from 1 to 3 with 1 = I still feel ill; 2 = I feel better; 3 = I feel healthy. Secondary efficacy endpoints were assessed twice daily at 12-hour intervals and recorded in the patient's diary from day 1 to the end of treatment (day 5 [adolescents] or day 7 [children]) for axillary temperature, antipyretics intake, and symptom-related endpoints, and from day 1 to

the closing visit (day 6 [adolescents] or day 8 [children]) for full recovery status.

Safety outcome measures and assessments

Safety-related endpoints included the incidence of adverse events (AEs), as recorded in the patient's diary during the treatment period, and physical examinations by the GP on days 1 and 6 (adolescents) or 8 (children).

Statistical analysis

The statistical analyses were done by an external blinded statistician. In both cohorts, a total number of 320 patients (160 per treatment group) were required to detect a difference of 5% between the two treatment groups with 80% power.

All patients who completed the treatment and all planned trial visits per protocol and did not have protocol deviations were included in the efficacy analyses. For the primary endpoint analysis, the 2-proportion Z-test was used to compare the percentages of clinically recovered patients between the active and placebo group. The mean disease duration in both groups was compared using an independent samples t-test. The secondary endpoints were analyzed using the same statistical methods as used for the primary endpoint analyses.

The safety analysis included all patients who received at least one dose of Aviron Rapid or a placebo. The incidence of AEs was summarized descriptively. All statistical tests were two-sided except for the 2-proportion Z-test. Statistical significance was set at $p<0.05$. All statistical analyses were performed using SPSS 17.

RESULTS

Patient disposition and baseline demographics

The trial started on 27 January 2020 (i.e., enrollment of the first patient in the trial) and was completed on 14 March 2020 (i.e., end of follow-up for the last patient in the trial). In total, 380 adolescents and 401 children were enrolled in the respective cohorts and randomly assigned to one of the two treatment groups. Safety analyses included all randomized patients. Efficacy analyses comprised 329 adolescents and 319 children. The reasons for excluding patients from the efficacy analysis are shown in **Fig. 1.**

Overall, in the adolescent cohort, the mean age was 14.6 years and 54% of patients were male. In the pediatric cohort, the mean age was 8.6 years and 51% of patients were male. Patient demographics were comparable in the two treatment groups in both cohorts. The total symptom severity score at baseline was slightly higher in the adolescent cohort (25.6 and 24.9 in the active and placebo group, respectively) compared with the pediatric cohort (24.6 and 23.5, respectively). The mean axillary temperature was

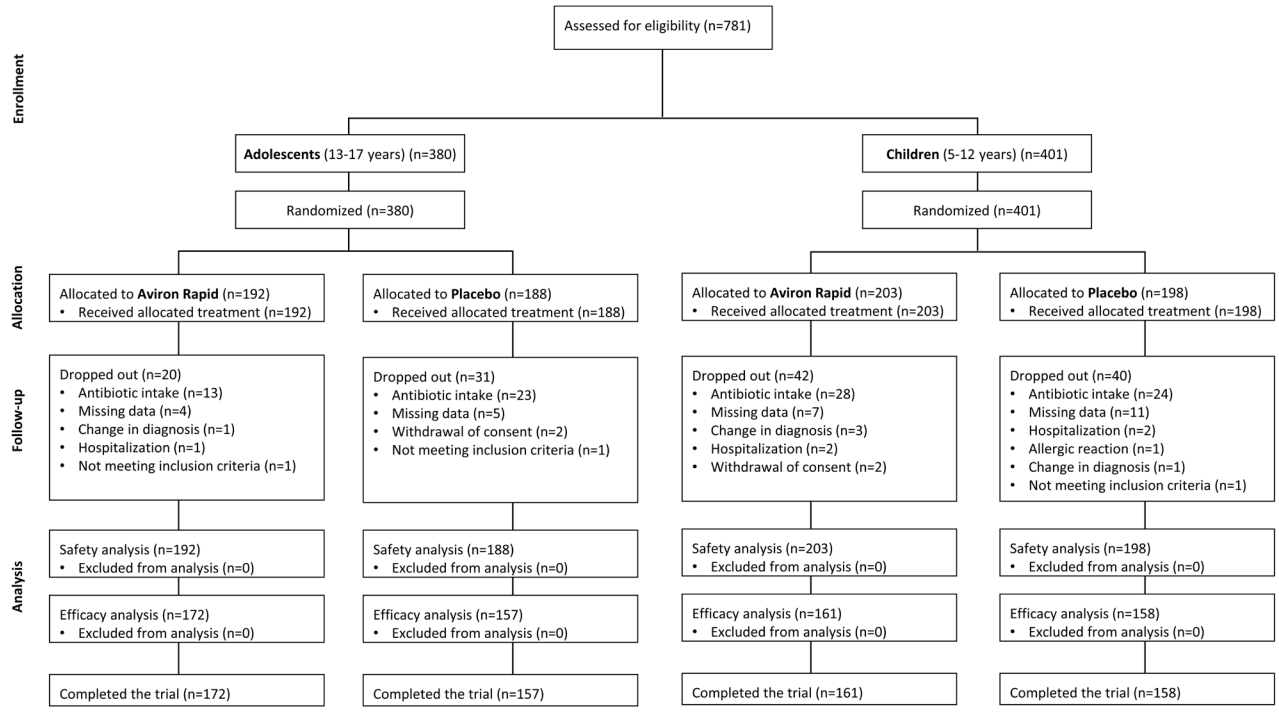

Figure 1. Patient disposition (Safety Analysis). Safety analysis included all patients who received at least one dose of Aviron Rapid or placebo. Efficacy analysis included all patients who completed treatment and all planned trial visits per protocol, and did not have protocol deviations.

38°C in the active and placebo groups in both cohorts. The percentages of patients reporting any symptom at baseline were generally lower in the pediatric cohort, compared with the adolescent cohort. Nasal congestion was the most common symptom in both cohorts (reported in >91% of adolescents and >88% of children). There were no significant differences between the active and placebo group in both cohorts **(Table 1)**.

For nasal congestion, cough, sore throat, headache, fatigue, and sleep disturbance, n (%) refers to the number (and percentage) of patients with a particular symptom at baseline; the mean values refer to the mean severity of a particular symptom at baseline.

Primary Endpoint

In the adolescent cohort, the percentages of patients meeting the criteria for clinical recovery were consistently higher in the active group compared with the placebo group from 24 hours after initiation of treatment (i.e., morning of day 2: 8.1% versus 1.9%, respectively; p=0.0055) until the end of treatment (i.e., evening of day 5: 90.7% versus 80.9%; p=0.0052). Differences were statistically significant (p<0.05) as of the morning of day 2 onwards until end of treatment, except for the morning of day 4 (p=0.0786) **(Fig. 2)** (**Supplementary Table 1**) (see Appendix). The mean disease duration was significantly lower in the active group (75 h, 95% CI: 70.80, 79.20) compared with the placebo group (85 h, 95% CI: 80.90, 89.10) (p=0.003) **(Fig. 3)**.

Similar results were obtained in the pediatric cohort with consistently higher percentages of clinically recovered patients in the active group compared with the placebo group from 24 hours after initiation of treatment (i.e., morning of day 2: 5.6% versus 4.4%, respectively; p=0.31) until end of treatment (i.e., evening of day 7: 98.8% versus 89.2%; p=0.001). Differences were statistically significant (p<0.05) as of the morning of day 3 and throughout the treatment period **(Fig. 2)** (**Supplementary Table 1**) (see Appendix). The mean disease duration was significantly lower in the active group (85 h, 95% CI: 79.50, 90.50) compared with the placebo group (101 h, 95% CI: 94.40, 107.60) (p=0.003) **(Fig. 3)**.

Secondary endpoints

Persistent decrease of temperature

From the morning of day 2 onwards until the end of treatment, the percentage of patients in the adolescent and pediatric cohorts with a persistent temperature decrease of <37°C was consistently higher in the active group than that in the placebo group, with the biggest difference between the two treatment groups being noticed on the morning

Table 1. Patient demographics and baseline symptoms (efficacy analysis)

Parameter	Statistics	Adolescents (13-17 years)		Children (5-12 years)	
		Active (Aviron Rapid) (n=172)	Placebo (n=157)	Active (Aviron Rapid) (n=161)	Placebo (n=158)
Age (years)	Mean	14.58	14.59	8.83	8.42
	95% CI	(14.29, 14.71)	(14.28, 14.72)	(8.50, 9.16)	(8.07, 8.75)
Male	n (%)	91 (52.9%)	87 (55.4%)	76 (47.2%)	86 (54.4%)
Total symptom severity score	Mean	25.6	24.9	24.6	23.5
	95% CI	(24.13, 27.10)	(23.28, 26.52)	(23.10, 26.10)	(21.93, 25.10)
Axillary temperature (°C)	Mean	38.15	38.11	38.09	38.23
	95% CI	(38.05, 38.25)	(38.01, 38.21)	(38.14, 38.34)	(38.00, 38.21)
Nasal congestion	n (%)	160 (93.0%)	143 (91.1%)	148 (91.9%)	140 (88.6%)
	Mean	4.71	4.67	5.01	4.76
Cough	n (%)	155 (90.1%)	142 (90.4%)	139 (86.3%)	142 (89.9%)
	Mean	4.74	4.90	5.25	4.65
Sore throat	n (%)	164 (95.3%)	151 (96.2%)	129 (80.1%)	125 (79.1%)
	Mean	5.22	5.19	5.36	5.62
Headache	n (%)	163 (94.8%)	143 (91.1%)	122 (75.8%)	129 (81.6%)
	Mean	4.83	4.63	4.87	4.79
Fatigue	n (%)	164 (95.3%)	149 (94.9%)	145 (90.1%)	139 (88.0%)
	Mean	5.48	5.25	5.19	4.98
Sleep disturbance	n (%)	114 (66.3%)	108 (68.8%)	109 (67.7%)	89 (56.3%)
	Mean	3.26	2.88	3.47	3.12

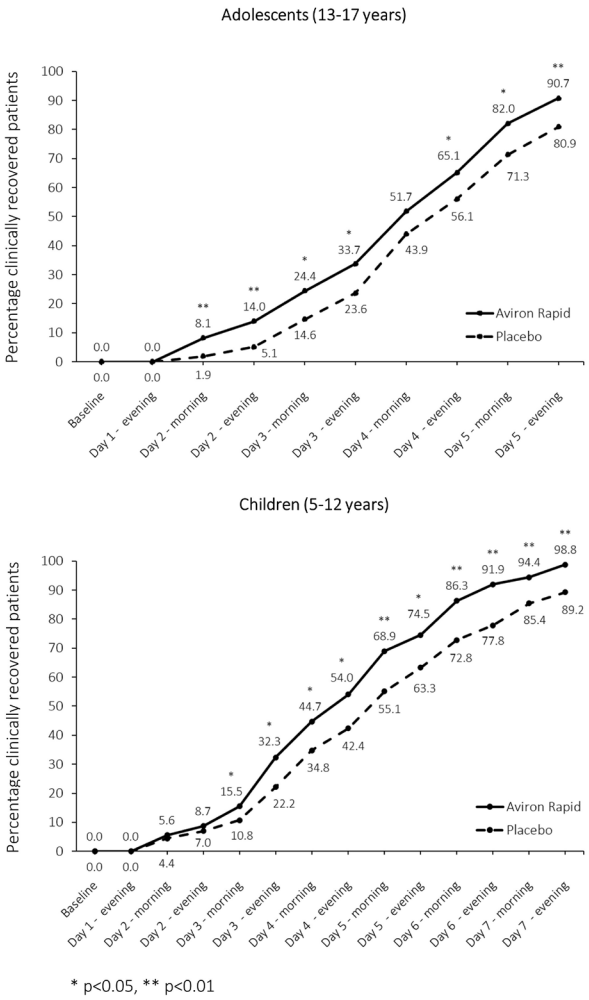

Figure 2. Primary endpoint: percentage clinically recovered patients (Efficacy Analysis). *P*-values from 1-sided 2-proportion Z-test.

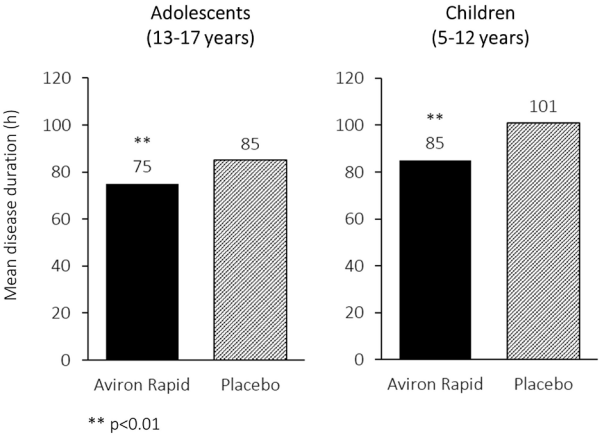

Figure 3. Primary endpoint: mean disease duration (Efficacy Analysis). *P*-values from 2-sided independent samples T-test.

of day 5 in adolescents (90.7% versus 77.7%; $p<0.001$) and on the evening of day 3 in children (58.4% versus 38.6%; $p=0.001$) **(Fig. 4)** (**Supplementary Table 2**) (see Appendix). In both cohorts, the mean time to persistent decrease of temperature was significantly lower in the active group compared with the placebo group (65 h, 95% CI: 60.80, 69.20 vs. 74 h, 95% CI: 69.30, 78.70 in adolescents [$p=0.005$] and 48 h, 95% CI: 42.50, 53.50 vs. 72 h, 95% CI: 65.80, 78.20 in children [$p=0.001$]) **(Fig. 5)**.

Antipyretics use

The percentage of adolescent patients taking antipyretics was consistently lower in the active group compared with the placebo group from the evening of day 1 onwards until the end of treatment. In the pediatric cohort, statistically significantly lower percentages of patients on antipyretics were observed as of the morning of day 3 until the end of treatment **(Fig. 6) (Supplementary Table 3)** (see Appendix). The mean duration of antipyretics intake was signifi-

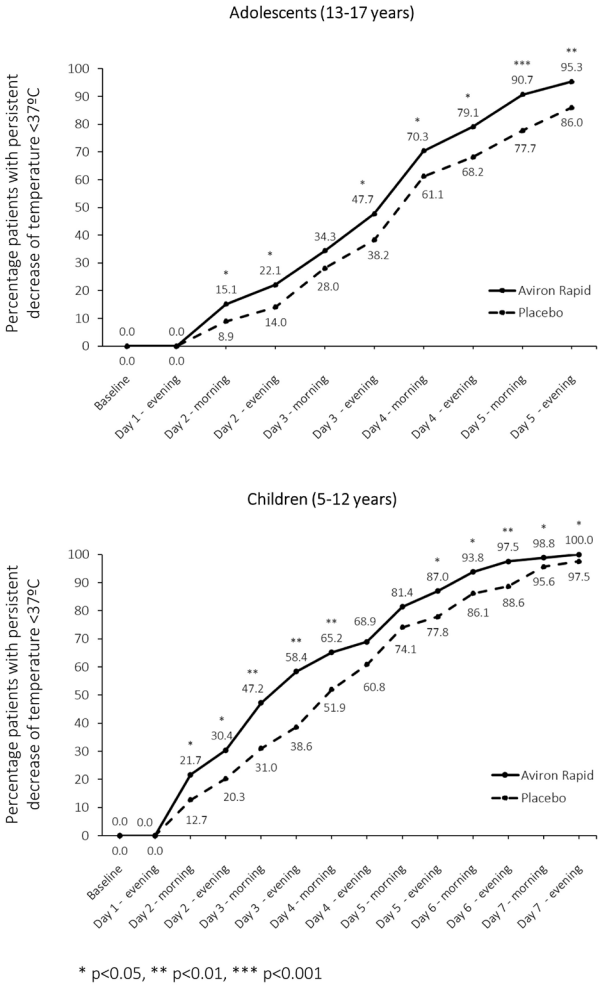

Figure 4. Secondary endpoints: Percentage of patients with persistent decrease of temperature <37°C (Efficacy Analysis). *P*-values from 1-sided 2-proportion Z-test.

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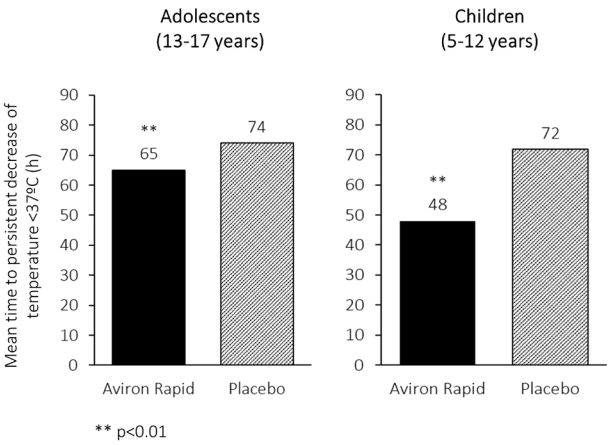

Figure 5. Secondary endpoints: mean time to persistent decrease of temperature <37°C (Efficacy Analysis). *P*-values from 2-sided independent samples T-test.

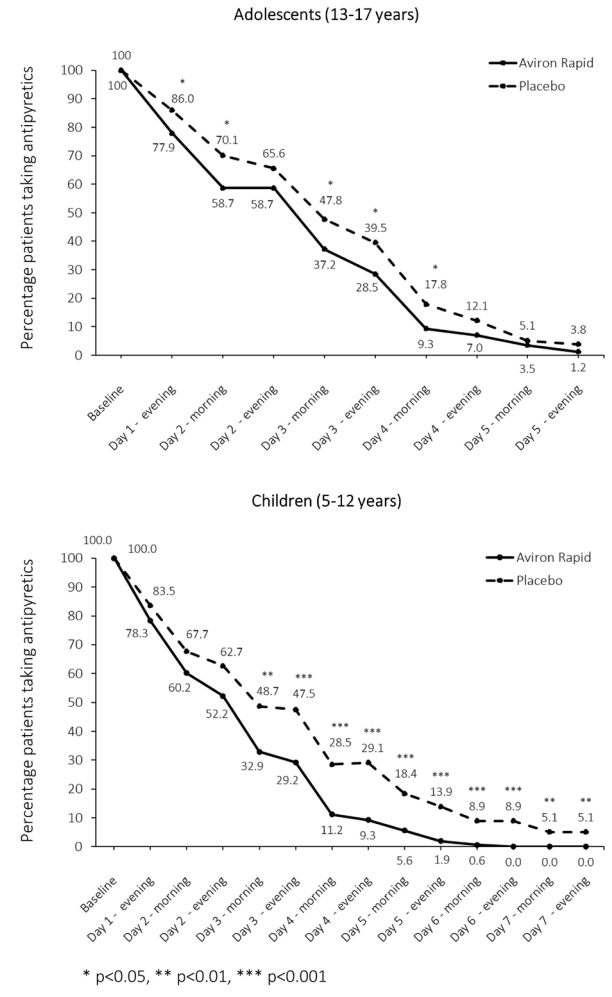

Figure 6. Secondary endpoints: percentage of patients taking antipyretics (Efficacy Analysis). *P*-values from 1-sided 2-proportion Z test for adolescents and 2-sided Pearson chi-square test for children.

cantly lower in the active group compared with the placebo group, both in the adolescent cohort (50 h, 95% CI: 45.90, 54.10 vs. 58 h, 95% CI: 53.60, 62.30; p=0.007) and in the pediatric cohort (43 h, 95% CI: 39.40, 46.60 vs. 62 h, 95% CI: 56.00, 68.00; p<0.001) **(Fig. 7)**.

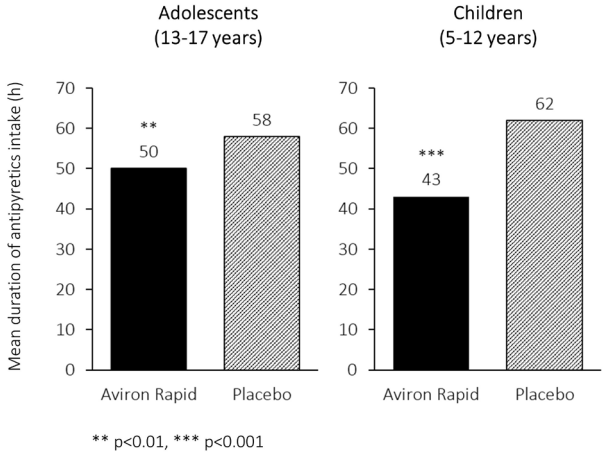

Figure 7. Secondary endpoints: mean duration of antipyretics intake (Efficacy Analysis). *P*-values from 2-sided independent samples T-test.

Symptom severity

The mean total severity of clinical symptoms in the adolescents in the active group was consistently lower than that in the placebo group from the evening of day 1 until the end of treatment, with day 3 showing the biggest difference between the two groups **(Supplementary Table 4)** (see Appendix). For nasal congestion, cough, and sleep disturbance, the percentages of adolescents with persistent improvement were consistently higher in the active group compared with the placebo group throughout the entire treatment period. As of the morning of day 2 until the end of treatment, a higher percentage of patients in the active group had persistent improvement of sore throat compared with the placebo group. No relevant differences between the two groups were observed for headache and fatigue **(Supplementary Tables 5–10)** (see Appendix).

Among children in the active group, the mean total severity of clinical symptoms was consistently lower than that of the placebo group as of the morning of day 3 until the end of treatment. Before that time point, the mean total score was higher in the placebo group **(Supplementary Table 4)** (see Appendix). A similar pattern was observed for the individual symptoms nasal of congestion and cough, for which statistically significantly higher percentages of children with persistent improvement in the active group were only observed from day 5 (for nasal congestion) or day 6 (for cough) onwards. For fatigue, sore throat, and sleep disturbance, the percentages of children with persistent improvement were consistently higher in the active group compared with the placebo group as of the evening of day 1 or the morning of

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day 2 and throughout the entire treatment period. The largest difference between the two groups was observed on days 3 and 4 for fatigue and sleep disturbance, and on days 4 and 5 for sore throat. For headache, similar percentages were observed in both groups throughout the treatment period until the morning of day 6. As of the evening of day 6 until the end of treatment, significantly higher percentages of patients in the active group had persistent improvement of headache compared with the placebo group **(Supplementary Tables 5–10)** (see Appendix).

The percentage of adolescents and children being considered fully recovered was consistently higher in the active group as of the evening of day 2 or the evening of day 1, respectively, until nearly all patients in both groups reached full recovery by the end of treatment **(Supplementary Table 11)** (see Appendix).

Safety endpoints

In both cohorts, the incidence of AEs was similar in the active and placebo groups. No serious AEs were reported. In the adolescent cohort, 14 (7.3%) patients in the active group and 23 (12.2%) in the placebo group reported AEs, the most common being antibiotic treatment for unknown reason (reported in 13 [6.8%] and 17 [9.0%] patients, respectively). In the pediatric cohort, 30 (14.8%) and 27 (13.6%) patients in the active and placebo group, respectively, reported AEs, the most common also being antibiotic treatment for unknown reason (in 20 [9.9%] and 18 [9.1%] patients, respectively) **(Table 2)**. Only one child in the placebo group experienced an AE of allergic reaction, and one adolescent (in the active group) and four children (2 in each treatment group) were hospitalized. No clinically relevant findings were reported for physical examinations.

DISCUSSION

Acute upper respiratory tract infections are a major cause of morbidity and one of the most frequent reasons for children and adults to visit GP offices. Given that the majority of AURTIs have a viral etiology, their management is often limited to symptomatic medications. However, there is no conclusive evidence that these medications also shorten symptom duration.[16,17] Moreover, the use of over-the-counter medications for AURTIs in children is often limited given the higher risk of side effects.[18] The rapid evolvement of certain viruses to escape human immunity limits the efficacy of antivirals and complicates the development of vaccines. Given the major burden AURTIs have on society due to missed work and (unnecessary) medical care and the emergence of new viruses potentially giving rise to major outbreaks or even pandemics, novel approaches with efficacy against a broad range of common viruses are urgently needed. In this trial, an alternative approach in the management of AURTIs was evaluated, relying on the potential synergistic activity of three naturally occurring ingredients with demonstrated in vitro and in vivo antiviral effects. Aviron Rapid is a dietary supplement approved for human use containing andrographolide, proprietary spirulina extract, and humic acid, which have the potential to target viral replication at different levels, including viral cell surface attachment[19], viral envelope fusion to the endosomal membrane[20], viral RNA polymerase endonuclease activity[21], and intracellular viral particle transport[22]. The clinical benefit of Aviron Rapid in the management of AURTIs in adolescents and children was supported by results obtained in the adult cohort of this trial[10], which demonstrated that daily use of Aviron Rapid for 5 days decreases disease duration, intake of antipyretics, and symptom severity. Significant differences were observed as early as 12 or 24 hours after initiation of treatment.

This clinical trial demonstrated that daily use of Aviron Rapid for 5 (adolescents) or 7 (children) days in combination with standard symptomatic therapy resulted in a significantly shorter duration of disease compared with placebo. The percentage of clinically recovered patients was significantly higher in adolescents and children on Aviron Rapid than in those on placebo from 24 and 48 hours after start of treatment, respectively. Aviron Rapid intake

Table 2. Incidence of adverse events (safety analysis)

	Adolescents (13-17 years)		Children (5-12 years)	
	Active (Aviron Rapid) (n=192)	Placebo (n=188)	Active (Aviron Rapid) (n=203)	Placebo (n=198)
Any adverse event, n (%)	14 (7.3%)	23 (12.2%)	30 (14.8%)	27 (13.6%)
Antibiotic treatment for unknown reason	13 (6.8%)	17 (9.0%)	20 (9.9%)	18 (9.1%)
Bronchitis	0 (0%)	2 (1.1%)	6 (3.0%)	4 (2.0%)
Hospitalization	1 (0.5%)	0 (0%)	2 (1.0%)	2 (1.0%)
Otitis	0 (0%)	2 (1.1%)	1 (0.5%)	1 (0.5%)
Laryngitis	0 (0%)	1 (0.5%)	1 (0.5%)	0 (0%)
Acute tonsillitis	0 (0%)	1 (0.5%)	0 (0%)	1 (0.5%)
Allergic reaction	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)

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significantly reduced the duration of fever (i.e., an axillary temperature >37°C) and the duration of antipyretics intake. As early as 24 hours after start of treatment, a significantly higher percentage of adolescents and children on Aviron Rapid achieved persistent decrease of temperature <37°C. The effect of Aviron Rapid treatment on symptom relief was generally more pronounced in adolescents than in children. Remarkably, throughout the entire treatment period, a higher percentage of adolescents on Aviron Rapid experienced relief of nasal congestion, cough, and sleep disturbance compared with placebo. In children, a similar beneficial effect on nasal congestion and cough was observed, though it became apparent later in the course of disease (i.e. by days 5 and 6, respectively). The largest difference in percentage of patients with relief of sore throat between the Aviron Rapid and placebo group was observed on days 3 and 4 for adolescents and on days 4 and 5 for children.

Across both cohorts, a low number of AEs was reported and no major differences in the incidence of individual AEs were observed between the two treatment groups.

The results of this trial confirm the promising results previously obtained with Aviron Rapid in adults[10] and warrant further research into the potential synergistic effects of the three active ingredients in Aviron Rapid in the management of viral AURTIs. The therapeutic potential of Aviron Rapid in this age group is further supported by the fact that children are even more susceptible to AURTIs than adults are.

Given that the standard approach to managing AURTIs in contemporary outpatient practice does not include testing to identify the infectious agent, one limitation of this trial was the lack of confirmation of the viral etiology of the AURTIs. Moreover, it cannot be guaranteed that the trial included only patients who visited their general practitioner's office within 24 hours of the onset of their first symptom. Another limitation of the trial was the relatively small sample size.

CONCLUSIONS

The results of this trial in adolescents and children confirms previous data reporting on the efficacy of Aviron Rapid, a dietary supplement containing andrographolide, proprietary spirulina extract, and humic acid, in the management of AURTIs in adults. Aviron Rapid treatment rapidly increased the number of clinically recovered patients and reduced overall disease duration and duration of symptoms, in particular fever, while being well tolerated.

Ethics approval and consent to participate

The trial protocol and informed consent were approved by the Ethics Committee of the First Pediatric Consultative Clinic, Ltd, Bulgaria (on November 30, 2019, ref No. 033/30.10.2019). The trial was conducted in accordance with the Declaration of Helsinki, the protocol, the International Council for Harmonisation for Good Clinical Practice Guideline E6 (R2), and local ethical and legal requirements. Written informed consent was obtained from all patients' parents prior to trial entry.

Consent for publication

Not applicable

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article (and the Supplementary Tables).

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

Conceptualization of the trial: R.M.M., I.S.T, and L.N.; Trial methodology: R.M.M., I.S.T, and L.N.; Investigation of participants: R.M.M., I.S.T, P.P., and A.M.; Supervision of the trial: R.M.M. and I.S.T.; Validation of trial data: P.P. and R.M.M.; Project administration: A.M.; Visualization of trial data: I.S.T., R.M.M., and P.P.; Resources: L.N.; Data curation, Formal analysis, Software: V.H. All authors contributed to data analysis, drafting, and revising the manuscript. All authors reviewed and approved the final manuscript.

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Appendix

Supplementary tables

Additional tables which present results of the trial not included in the body of the manuscript.

Supplementary Table 1. Primary endpoint: number and percentage of clinically recovered patients (Efficacy Analysis)

Time Point	Active (Aviron Rapid)		Placebo		*P*-value[a]
	n cumulative	% cumulative	n cumulative	% cumulative	
Adolescents (13-17 years)	N=172		N=157		
Initial visit/Baseline	0	0.0	0	0.0	-
Day 1 - evening	0	0.0	0	0.0	-
Day 2 - morning	14	8.1	3	1.9	**0.0055**
Day 2 - evening	24	14.0	8	5.1	**0.0033**
Day 3 - morning	42	24.4	23	14.6	**0.0128**
Day 3 - evening	58	33.7	37	23.6	**0.0217**
Day 4 - morning	89	51.7	69	43.9	0.0786
Day 4 - evening	112	65.1	88	56.1	**0.0474**
Day 5 - morning	141	82.0	112	71.3	**0.0107**
Day 5 - evening	156	90.7	127	80.9	0.0052
Children (5-12 years)	N=161		N=158		
Initial visit/Baseline	0	0.0	0	0.0	-
Day 1 - evening	0	0.0	0	0.0	-
Day 2 - morning	9	5.6	7	4.4	0.31
Day 2 - evening	14	8.7	11	7.0	0.28
Day 3 - morning	25	15.5	17	10.8	**0.01**
Day 3 - evening	52	32.3	35	22.2	**0.02**
Day 4 - morning	72	44.7	55	34.8	**0.03**
Day 4 - evening	87	54.0	67	42.4	**0.01**
Day 5 - morning	111	68.9	87	55.1	**0.005**
Day 5 - evening	120	74.5	100	63.3	**0.01**
Day 6 - morning	139	86.3	115	72.8	**0.001**
Day 6 - evening	148	91.9	123	77.8	**0.001**
Day 7 - morning	152	94.4	135	85.4	**0.003**
Day 7 - evening	159	98.8	141	89.2	**0.001**

[a] *P*-values from 1-sided 2-proportion Z test. Values in bold are statistically significant ($p<0.05$).

Supplementary Table 2. Secondary endpoint: number and percentage of patients with persistent decrease of temperature <37°C (Efficacy Analysis)

Time Point	Active (Aviron Rapid)		Placebo		*P*-value[a]
	n cumulative	% cumulative	n cumulative	% cumulative	
Adolescents (13-17 years)	N=172		N=157		
Initial visit/Baseline	0	0.0	0	0.0	-
Day 1 - evening	0	0.0	0	0.0	-
Day 2 - morning	26	15.1	14	8.9	**0.0427**
Day 2 - evening	38	22.1	22	14.0	**0.0287**
Day 3 - morning	59	34.3	44	28.0	0.1092
Day 3 - evening	82	47.7	60	38.2	**0.0411**
Day 4 - morning	121	70.3	96	61.1	**0.0393**
Day 4 - evening	136	79.1	107	68.2	**0.0173**
Day 5 - morning	156	90.7	122	77.7	<0.001
Day 5 - evening	164	95.3	135	86.0	**0.0017**
Children (5-12 years)	N=161		N=158		
Initial visit/Baseline	0	0.0	0	0.0	-
Day 1 - evening	0	0.0	0	0.0	-
Day 2 - morning	35	21.7	20	12.7	**0.016**
Day 2 - evening	49	30.4	32	20.3	**0.019**
Day 3 - morning	76	47.2	49	31.0	**0.001**
Day 3 - evening	94	58.4	61	38.6	**0.001**
Day 4 - morning	105	65.2	82	51.9	**0.008**
Day 4 - evening	111	68.9	96	60.8	0.064
Day 5 - morning	131	81.4	117	74.1	0.051
Day 5 - evening	140	87.0	123	77.8	**0.015**
Day 6 - morning	151	93.8	136	86.1	**0.011**
Day 6 - evening	157	97.5	140	88.6	**0.001**
Day 7 - morning	159	98.8	151	95.6	**0.041**
Day 7 - evening	161	100.0	154	97.5	**0.021**

[a] ***P***-values from 1-sided 2-proportion Z test. Values in bold are statistically significant ($p<0.05$).

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Supplementary Table 3. Secondary endpoint: number and percentage of patients taking antipyretics (Efficacy Analysis)

Time Point	Active (Aviron Rapid)		Placebo		*P*-value[a]
	n cumulative	% cumulative	n cumulative	% cumulative	
Adolescents (13-17 years)	N=172		N=157		
Initial visit/Baseline	172	100.0	157	100.0	-
Day 1 - evening	134	77.9	135	86.0	**0.0287**
Day 2 - morning	101	58.7	110	70.1	**0.0156**
Day 2 - evening	101	58.7	103	65.6	0.0989
Day 3 - morning	64	37.2	75	47.8	**0.0259**
Day 3 - evening	49	28.5	62	39.5	**0.0175**
Day 4 - morning	16	9.3	28	17.8	**0.0175**
Day 4 - evening	12	7.0	19	12.1	0.0570
Day 5 - morning	6	3.5	8	5.1	0.2365
Day 5 - evening	2	1.2	6	3.8	0.0634
Children (5-12 years)	N=161		N=158		
Initial visit/Baseline	161	100.0	158	100.0	-
Day 1 - evening	126	78.3	132	83.5	0.230
Day 2 - morning	97	60.2	107	67.7	0.165
Day 2 - evening	84	52.2	99	62.7	0.058
Day 3 - morning	53	32.9	77	48.7	**0.004**
Day 3 - evening	47	29.2	75	47.5	**< 0.001**
Day 4 - morning	18	11.2	45	28.5	**< 0.001**
Day 4 - evening	15	9.3	46	29.1	**< 0.001**
Day 5 - morning	9	5.6	29	18.4	**< 0.001**
Day 5 - evening	3	1.9	22	13.9	**< 0.001**
Day 6 - morning	1	0.6	14	8.9	**< 0.001**
Day 6 - evening	0	0.0	14	8.9	**< 0.001**
Day 7 - morning	0	0.0	8	5.1	**0.004**
Day 7 - evening	0	0.0	8	5.1	**0.004**

[a] *P*-values from 1-sided 2-proportion Z test for adolescents and 2-sided Pearson Chi-Square test for children. Values in bold are statistically significant ($p<0.05$).

Supplementary Table 4. Secondary endpoint: mean total severity of clinical symptoms (Efficacy Analysis)

Time Point	Active (Aviron Rapid)	Placebo	*P*-value[a]
Adolescents (13-17 years)	N=172	N=157	
Initial visit/Baseline	25.6	24.9	0.515
Day 1 - evening	25.4	26.0	0.625
Day 2 - morning	22.4	23.8	0.238
Day 2 - evening	20.0	21.5	0.215
Day 3 - morning	14.6	17.2	**0.017**
Day 3 - evening	12.6	14.8	**0.041**
Day 4 - morning	9.3	10.6	0.149
Day 4 - evening	7.3	8.5	0.159
Day 5 - morning	5.3	6.2	0.171
Day 5 - evening	3.6	4.8	0.071
Children (5-12 years)	N=161	N=158	
Initial visit/Baseline	24.6	23.5	0.304
Day 1 - evening	25.4	24.0	0.239
Day 2 - morning	22.0	21.4	0.655
Day 2 - evening	20.1	19.6	0.663
Day 3 - morning	16.5	16.6	0.93
Day 3 - evening	14.6	15.8	0.271
Day 4 - morning	11.4	13.2	0.077
Day 4 - evening	10.0	11.7	0.094
Day 5 - morning	7.5	9.2	**0.034**
Day 5 - evening	6.9	7.8	0.233
Day 6 - morning	5.3	6.8	**0.028**
Day 6 - evening	4.3	5.4	0.07
Day 7 - morning	3.1	4.2	**0.034**
Day 7 - evening	2.2	3.4	**0.009**

[a] *P*-values from 2-sided independent samples T-test. Values in bold are statistically significant ($p<0.05$).

Symptom severity was measured on a visual analogue scale (VAS) for adolescents or a modified face pain scale (FPS-R) for children; the total score ranged from 0 to 60.

Supplementary Table 5. Secondary endpoint: number and percentage of patients without nasal congestion (Efficacy Analysis)

Time Point	Active (Aviron Rapid)		Placebo		*P*-value[a]
	n cumulative	% cumulative	n cumulative	% cumulative	
Adolescents (13-17 years)	N=160		N=143		
Initial visit/Baseline	0	0.0	0	0.0	-
Day 1 - evening	20	12.5	9	6.3	**0.0335**
Day 2 - morning	22	13.8	12	8.4	0.0688
Day 2 - evening	32	20.0	15	10.5	**0.0113**
Day 3 - morning	44	27.5	24	16.8	**0.0129**
Day 3 - evening	54	33.8	33	23.1	**0.0200**
Day 4 - morning	74	46.3	55	38.5	0.0852
Day 4 - evening	96	60.0	68	47.6	**0.0153**
Day 5 - morning	120	75.0	90	62.9	0.0113
Day 5 - evening	133	83.1	99	69.2	**0.0022**
Children (5-12 years)	N=148		N=140		
Initial visit/Baseline	0	0.0	0	0.0	-
Day 1 - evening	9	6.1	11	7.9	0.72
Day 2 - morning	10	6.8	13	9.3	0.78
Day 2 - evening	14	9.5	15	10.7	0.63
Day 3 - morning	19	12.8	26	18.6	0.91
Day 3 - evening	31	20.9	30	21.4	0.54
Day 4 - morning	50	33.8	43	30.7	0.29
Day 4 - evening	63	42.6	54	38.6	0.24
Day 5 - morning	84	56.8	68	48.6	0.08
Day 5 - evening	91	61.5	73	52.1	0.05
Day 6 - morning	105	70.9	82	58.6	**0.01**
Day 6 - evening	118	79.7	97	69.3	**0.02**
Day 7 - morning	128	86.5	108	77.1	**0.01**
Day 7 - evening	136	91.9	116	82.9	**0.01**

[a] *P*-values from 1-sided 2 proportion Z-test. Values in bold are statistically significant ($p<0.05$).

Only patients experiencing this symptom at baseline were included in the analysis.

Symptom severity was measured on a VAS (for adolescents) or FPS-R (for children), both ranging from 0 to 10.

Supplementary Table 6. Secondary endpoint: number and percentage of patients without cough (Efficacy Analysis)

Time Point	Active (Aviron Rapid)		Placebo		*P*-value[a]
	n cumulative	% cumulative	n cumulative	% cumulative	
Adolescents (13-17 years)	N=155		N=142		
Initial visit/Baseline	0	0.0	0	0.0	-
Day 1 - evening	24	15.5	14	9.9	0.0747
Day 2 - morning	29	18.7	17	12.0	0.0555
Day 2 - evening	37	23.9	20	14.1	**0.0161**
Day 3 - morning	47	30.3	24	16.9	**0.0034**
Day 3 - evening	54	34.8	32	22.5	**0.0098**
Day 4 - morning	71	45.8	49	34.5	**0.0237**
Day 4 - evening	83	53.5	65	45.8	0.0925
Day 5 - morning	108	69.7	85	59.9	**0.0385**
Day 5 - evening	123	79.4	102	71.8	0.0634
Children (5-12 years)	N=139		N=142		
Initial visit/Baseline	0	0.0	0	0.0	-
Day 1 - evening	5	3.6	5	3.5	0.48
Day 2 - morning	6	4.3	10	7.0	0.83
Day 2 - evening	10	7.2	12	8.5	0.65
Day 3 - morning	11	7.9	17	12.0	0.87
Day 3 - evening	19	13.7	22	15.5	0.66
Day 4 - morning	34	24.5	35	24.6	0.51
Day 4 - evening	42	30.2	46	32.4	0.65
Day 5 - morning	59	42.4	58	40.8	0.39
Day 5 - evening	68	48.9	66	46.5	0.34
Day 6 - morning	83	59.7	73	51.4	0.08
Day 6 - evening	98	70.5	85	59.9	**0.03**
Day 7 - morning	113	81.3	101	71.1	**0.02**
Day 7 - evening	124	89.2	111	78.2	**0.01**

[a] *P*-values from 1-sided 2 proportion Z-test. Values in bold are statistically significant ($p<0.05$).

Only patients experiencing this symptom at baseline were included in the analysis.

Symptom severity was measured on a VAS (for adolescents) or FPS-R (for children), both ranging from 0 to 10.

Supplementary Table 7. Secondary endpoint: number and percentage of patients without sore throat (Efficacy Analysis)

Time Point	Active (Aviron Rapid)		Placebo		*P*-value[a]
	n cumulative	% cumulative	n cumulative	% cumulative	
Adolescents (13-17 years)	N=164		N=151		
Initial visit/Baseline	0	0.0	0	0.0	-
Day 1 - evening	20	12.2	19	12.6	0.5429
Day 2 - morning	31	18.9	28	18.5	0.4638
Day 2 - evening	45	27.4	40	26.5	0.4287
Day 3 - morning	67	40.9	49	32.5	0.0613
Day 3 - evening	84	51.2	61	40.4	**0.0273**
Day 4 - morning	119	72.6	92	60.9	0.0137
Day 4 - evening	131	79.9	107	70.9	**0.0316**
Day 5 - morning	143	87.2	127	84.1	0.2161
Day 5 - evening	154	93.9	139	92.1	0.2653
Children (5-12 years)	N=129		N=125		
Initial visit/Baseline	0	0.0	0	0.0	-
Day 1 - evening	15	11.6	15	12.0	0.54
Day 2 - morning	23	17.8	21	16.8	0.42
Day 2 - evening	32	24.8	26	20.8	0.22
Day 3 - morning	50	38.8	46	36.8	0.37
Day 3 - evening	64	49.6	57	45.6	0.26
Day 4 - morning	85	65.9	68	54.4	**0.03**
Day 4 - evening	98	76.0	79	63.2	**0.01**
Day 5 - morning	107	82.9	89	71.2	**0.01**
Day 5 - evening	113	87.6	98	78.4	**0.02**
Day 6 - morning	121	93.8	109	87.2	**0.03**
Day 6 - evening	122	94.6	114	91.2	0.14
Day 7 - morning	127	98.4	118	94.4	**0.04**
Day 7 - evening	128	99.2	122	97.6	0.15

[a] *P*-values from 1-sided 2 proportion Z-test. Values in bold are statistically significant ($p<0.05$).

Only patients experiencing this symptom at baseline were included in the analysis.

Symptom severity was measured on a VAS (for adolescents) or FPS-R (for children), both ranging from 0 to 10.

Supplementary Table 8. Secondary endpoint: number and percentage of patients without headache (Efficacy Analysis)

Time Point	Active (Aviron Rapid)		Placebo		*P*-value[a]
	n cumulative	% cumulative	n cumulative	% cumulative	
Adolescents (13-17 years)	N=163		N=143		
Initial visit/Baseline	0	0.0	0	0.0	-
Day 1 - evening	23	14.1	22	15.4	0.6256
Day 2 - morning	41	25.2	36	25.2	0.5000
Day 2 - evening	61	37.4	46	32.2	0.1706
Day 3 - morning	96	58.9	77	53.8	0.1846
Day 3 - evening	112	68.7	91	63.6	0.1732
Day 4 - morning	130	79.8	111	77.6	0.3193
Day 4 - evening	142	87.1	119	83.2	0.1684
Day 5 - morning	151	92.6	132	92.3	0.4605
Day 5 - evening	158	96.9	135	94.4	0.1402
Children (5-12 years)	N=122		N=129		
Initial visit/Baseline	0	0.0	0	0.0	-
Day 1 - evening	13	10.7	19	14.7	0.82
Day 2 - morning	35	28.7	40	31.0	0.65
Day 2 - evening	52	42.6	55	42.6	0.5
Day 3 - morning	74	60.7	73	56.6	0.25
Day 3 - evening	83	68.0	83	64.3	0.26
Day 4 - morning	98	80.3	96	74.4	0.13
Day 4 - evening	104	85.2	103	79.8	0.13
Day 5 - morning	112	91.8	116	89.9	0.3
Day 5 - evening	113	92.6	118	91.5	0.37
Day 6 - morning	117	95.9	120	93.0	0.15
Day 6 - evening	120	98.4	121	93.8	**0.03**
Day 7 - morning	122	100.0	124	96.1	**0.01**
Day 7 - evening	122	100.0	126	97.7	**0.04**

[a] *P*-values from 1-sided 2 proportion Z-test. Values in bold are statistically significant ($p<0.05$).

Only patients experiencing this symptom at baseline were included in the analysis.

Symptom severity was measured on a VAS (for adolescents) or FPS-R (for children), both ranging from 0 to 10.

Supplementary Table 9. Secondary endpoint: number and percentage of patients without fatigue (Efficacy Analysis)

Time Point	Active (Aviron Rapid)		Placebo		*P*-value[a]
	n cumulative	% cumulative	n cumulative	% cumulative	
Adolescents (13-17 years)	N=164		N=149		
Initial visit/Baseline	0	0.0	0	0.0	-
Day 1 - evening	20	8.5	17	8.7	0.5251
Day 2 - morning	44	18.3	34	21.5	0.7609
Day 2 - evening	61	28.0	58	27.5	0.4607
Day 3 - morning	96	46.3	98	47.7	0.5979
Day 3 - evening	136	59.8	143	55.0	0.1955
Day 4 - morning	190	76.2	196	73.2	0.2708
Day 4 - evening	228	84.1	225	81.9	0.3022
Day 5 - morning	265	93.3	257	89.3	0.1038
Day 5 - evening	282	94.5	275	93.3	0.3285
Children (5-12 years)	N=145		N=139		
Initial visit/Baseline	0	0.0	0	0.0	-
Day 1 - evening	12	8.3	8	5.8	0.21
Day 2 - morning	31	21.4	23	16.5	0.14
Day 2 - evening	49	33.8	36	25.9	0.07
Day 3 - morning	79	54.5	61	43.9	**0.03**
Day 3 - evening	90	62.1	70	50.4	**0.02**
Day 4 - morning	112	77.2	92	66.2	**0.02**
Day 4 - evening	119	82.1	99	71.2	**0.01**
Day 5 - morning	128	88.3	113	81.3	**0.04**
Day 5 - evening	131	90.3	121	87.1	0.19
Day 6 - morning	138	95.2	126	90.6	0.06
Day 6 - evening	140	96.6	131	94.2	0.16
Day 7 - morning	142	97.9	133	95.7	0.14
Day 7 - evening	144	99.3	135	97.1	0.08

[a] *P*-values from 1-sided 2 proportion Z-test. Values in bold are statistically significant ($p<0.05$).

Only patients experiencing this symptom at baseline were included in the analysis.

Symptom severity was measured on a VAS (for adolescents) or FPS-R (for children), both ranging from 0 to 10.

Supplementary Table 10. Secondary endpoint: number and percentage of patients without sleep disturbance (Efficacy Analysis)

Time Point	Active (Aviron Rapid)		Placebo		*P*-value[a]
	n cumulative	% cumulative	n cumulative	% cumulative	
Adolescents (13-17 years)	N=114		N=108		
Initial visit/Baseline	0	0.0	0	0.0	-
Day 1 - evening	39	34.2	32	29.6	0.2313
Day 2 - morning	51	44.7	42	38.9	0.1907
Day 2 - evening	65	57.0	58	53.7	0.3105
Day 3 - morning	83	72.8	69	63.9	0.0769
Day 3 - evening	88	77.2	75	69.4	0.0943
Day 4 - morning	101	88.6	84	77.8	**0.0154**
Day 4 - evening	103	90.4	89	82.4	**0.0406**
Day 5 - morning	107	93.9	97	89.8	0.1315
Day 5 - evening	110	96.5	102	94.4	0.2258
Children (5-12 years)	N=109		N=89		
Initial visit/Baseline	0	0.0	0	0.0	-
Day 1 - evening	8	7.3	6	6.7	0.43
Day 2 - morning	29	26.6	23	25.8	0.44
Day 2 - evening	46	42.2	35	39.3	0.33
Day 3 - morning	63	57.8	42	47.2	0.06
Day 3 - evening	72	66.1	47	52.8	**0.02**
Day 4 - morning	82	75.2	57	64.0	**0.04**
Day 4 - evening	91	83.5	70	78.7	0.19
Day 5 - morning	95	87.2	74	83.1	0.21
Day 5 - evening	97	89.0	76	85.4	0.22
Day 6 - morning	102	93.6	80	89.9	0.17
Day 6 - evening	107	98.2	83	93.3	**0.04**
Day 7 - morning	108	99.1	84	94.4	**0.02**
Day 7 - evening	109	100.0	86	96.6	**0.02**

[a] *P*-values from 1-sided 2 proportion Z-test. Values in bold are statistically significant ($p<0.05$).

Only patients experiencing this symptom at baseline were included in the analysis.

Symptom severity was measured on a VAS (for adolescents) or FPS-R (for children), both ranging from 0 to 10.

Supplementary Table 11. Secondary endpoint: number and percentage of patients considered fully recovered (Efficacy Analysis)

Time Point	Active (Aviron Rapid)		Placebo		*P*-value[a]
	n cumulative	% cumulative	n cumulative	% cumulative	
Adolescents (13-17 years)	N=172		N=157		
Initial visit/Baseline	0	0.0	0	0.0	-
Day 1 - evening	0	0.0	0	0.0	-
Day 2 - morning	55	32.0	32	20.4	0.0086
Day 2 - evening	107	62.2	71	45.2	**0.0010**
Day 3 - morning	125	72.7	95	60.5	**0.0094**
Day 3 - evening	148	86.0	131	83.4	0.2561
Day 4 - morning	162	94.2	141	89.8	0.0697
Day 4 - evening	168	97.7	151	96.2	0.2134
Day 5 - morning	171	99.4	155	98.7	0.2549
Day 5 - evening	172	100.0	157	100.0	-
Day 6 – morning (closing visit)	172	100.0	157	100.0	-
Children (5-12 years)	N=161		N=158		
Initial visit/Baseline	0	0.0	0	0.0	-
Day 1 - evening	31	19.3	27	17.1	0.305
Day 2 - morning	50	31.1	42	26.6	0.187
Day 2 - evening	82	50.9	66	41.8	0.051
Day 3 - morning	100	62.1	81	51.3	**0.025**
Day 3 - evening	124	77.0	104	65.8	**0.013**
Day 4 - morning	134	83.2	117	74.1	**0.023**
Day 4 - evening	143	88.8	130	82.3	**0.049**
Day 5 - morning	149	92.5	140	88.6	0.116
Day 5 - evening	156	96.9	145	91.8	**0.024**
Day 6 - morning	159	98.8	151	95.6	**0.041**
Day 6 - evening	161	100.0	156	98.7	0.073
Day 7 - morning	161	100.0	157	99.4	0.162
Day 7 - evening	161	100.0	158	100.0	-
Day 8 – morning (closing visit)	161	100.0	158	100.0	-

[a] *P*-values from 1-sided 2 proportion Z-test for adolescents and from 2-sided Pearson Chi-Square test for children. Values in bold are statistically significant ($p<0.05$).

A patient is considered fully recovered if he/she is scored 2 ('I feel better') or 3 ('I feel healthy') on a scale ranging from 1 to 3, with 1 indicating 'I still feel ill'.

Эффективность и безопасность препарата на Aviron Rapid® у подростков и детей с острой вирусной инфекцией верхних дыхательных путей: многоцентровое рандомизированное двойное слепое плацебо-контролируемое клиническое исследование

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Резюме

Введение: Острые инфекции верхних дыхательных путей (ОИВДП) связаны со значительным бременем для общества, связанным с медицинским обслуживанием и снижением производительности труда. Новые методы лечения, способные сократить продолжительность заболевания, обеспечивая облегчение симптомов и хорошую переносимость, являются неудовлетворённой медицинской потребностью.

Цель: Основная цель этого исследования заключалась в изучении эффективности и безопасности Aviron Rapid, пищевой добавки, содержащей андрографолид, запатентованную спирулину и гуминовую кислоту, при лечении ОИВДП у подростков и детей.

Материалы и методы: Это рандомизированное двойное слепое плацебо-контролируемое исследование проводилось в период с января 2020 г. по март 2020 г. в 85 врачебных кабинетах общей практики в Болгарии. Подростки (13–17 лет) и дети (5–12 лет) с клиническим диагнозом ОИВДП были рандомизированы для получения стандартной симптоматической терапии + Aviron Rapid или плацебо в течение 5 и 7 дней соответственно. Первичными конечными точками этого исследования были число (и процент) клинически выздоровевших пациентов и средняя продолжительность заболевания.

Результаты: В общей сложности 380 подростков и 401 ребёнок были включены в 2 возрастные когорты и случайным образом распределены для лечения препаратом Aviron Rapid или плацебо. Процент пациентов, отвечающих критериям клинического выздоровления, был значительно выше в группе Aviron Rapid по сравнению с группой плацебо через 24 и 48 часов после начала лечения у подростков и детей соответственно. Лечение Aviron Rapid значительно сократило продолжительность заболевания, лихорадки и приёма жаропонижающих средств как у подростков, так и у детей. По сравнению с плацебо, значительно более высокий процент подростков и детей, принимавших Aviron Rapid, достиг стойкого снижения температуры менее чем на 37° С уже через 24 часа после начала лечения. В целом было зарегистрировано небольшое количество нежелательных явлений, и не наблюдалось существенных различий в частоте отдельных нежелательных явлений между двумя группами лечения в обеих когортах.

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Заключение: Это клиническое исследование продемонстрировало эффективность препарата Aviron Rapid при лечении острых инфекций верхних дыхательных путей у подростков и детей. Лечение Aviron Rapid быстро увеличивало число клинически выздоровевших пациентов и уменьшало общую продолжительность заболевания и продолжительность симптомов, в частности лихорадки, при хорошей переносимости.

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Ключевые слова

противовирусные препараты, острые инфекции верхних дыхательных путей, андрографолид, патентованная спирулина, гуминовая кислота