STUDY PROTOCOL

Study Title

Aviron Rapid vs placebo in the management of acute upper respiratory tract infections.

Acronym

ARVP-AURTI

Protocol /serial number

R-AVI-19-CT-004

Sponsor:

Neopharm Bulgaria Ltd

Date:

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Study hypothesis

Acute upper respiratory tract infections (AURTI) are a common occurrence worldwide and pose a huge burden both in terms of morbidity and mortality across all age groups. Currently, there are very few and safe effective treatments available for routine use, especially in children. We hypothesise that Aviron Rapid® (647 mg tablet), a food/dietary supplement containing andrographolide (10 mg), proprietary spirulina extract (100 mg) and humic acid racemic mixture (250 mg) will prove to be an effective treatment for AURTI across 3 cohorts of subjects: adults (18 – 60 years old), adolescents (13 – 17 years old), and children (5 – 12 years old). We hypothesize that this supplement will reduce the duration of the illness, decrease antipyretic intake, and ameliorate secondary symptoms (like nasal congestion, cough, sore throat, headache, fatigue, sleep disturbances) in all 3 cohorts when compared to a placebo, and does not induce any side effects.

Study design

Multicenter, Double-Blind, Placebo-Controlled, Randomized Clinical Study

Condition

Reducing illness duration, antipyretic intake, and improve secondary symptoms of acute upper respiratory tract infections in all age groups, without inducing any side-effects.

Interventions

This trial will be conducted across three different cohorts of participants. Study 1 will include adults aged between 18 and 60 with a clinical diagnosis of acute upper respiratory tract infection of unknown origin; Study 2 will include adolescents aged between 13 and 17 with a clinical diagnosis of acute upper respiratory tract infection of unknown origin; and Study 3 will include children aged between 5 and 12 with a clinical diagnosis of acute upper respiratory tract infection of unknown origin.

Subject recruitment will be done across eighty-five General Practitioner (GP) practices. Patients who will present in said clinics with symptoms suggestive of AURTI of viral aetiology (as diagnosed clinically by the GP, without any confirmatory lab investigations), will be asked whether they are willing to participate in the trial. Those subjects who will satisfy the inclusion criteria and have no exclusion criteria, will be then randomly allocated to either the

treatment or the control group. The GP will take the patient's history, perform a full physical examination, and initiate a standardised treatment plan.

All the three Studies will include a treatment group, who will receive Aviron Rapid® (647 mg tablet), containing andrographolide (10 mg), proprietary spirulina extract (100 mg) and humic acid racemic mixture (250 mg); and a control group who will receive placebo tablets packaged in the same manner as test product to maintain double-blind.

To ensure randomisation, every package will have a unique number generated by a randomization software. The patients who will meet the trial inclusion criteria will be randomized by Randomsamp® software (Randomsapp™ Software, Varna, Bulgaria). Participants will be randomly allocated to either the treatment, or the control group.

The daily dosage regime of the two groups is summarised in the table below:

	Study 1 (18 to 60 years)	**Study 2 (13 to 17 years)**	**Study 3 (5 to 12 years)**
Day 1	3 tablets 3 times daily	3 tablets 3 times daily	2 tablets 3 times daily
Day 2	2 tablets 3 times daily	2 tablets 3 times daily	1 tablet 3 times daily
Day 3	1 tablet 3 times daily	1 tablet 3 times daily	1 tablet 3 times daily
Day 4	1 tablet 3 times daily	1 tablet 3 times daily	1 tablet 3 times daily
Day 5	1 tablet 3 times daily	1 tablet 3 times daily	1 tablet 3 times daily
Day 6	*Not applicable*	*Not applicable*	1 tablet 3 times daily
Day 7	*Not applicable*	*Not applicable*	1 tablet 3 times daily

The subjects included in the trial, will then be given a diary, in which they will record data (including axillary temperature, antipyretics intake and symptoms severity evaluated by Visual Analogue Scale (VAS) twice daily, in the morning and in the evening, for 5 (Study 1 and Study 2) or 7 (Study 3) consecutive dates.

At Day 6 (Study 1 and Study 2) or 8 (Study 3), the subject enrolled in the trial will return to the GP Clinic. The doctor will then re-examine the patient and verify the completeness of the data in each subjects' dairy.

The main aim of this study is to then compare the results obtained in each group to verify the effectiveness of Aviron Rapid® across all age groups. Of particular interest will be to

investigate whether this drug will decrease the disease duration; reduce fever and antipyretic intake; and ameliorate symptoms in any or all of the 3 cohorts studied, and whether there will be any difference in response between the three groups.

Intervention Type

Supplement

Primary outcome measure

The primary outcome will be the number of clinically recovered patients as well as the average disease duration in all 3 studies.

The number of clinically recovered patients: to be considered "Clinically recovered", the subjects will have the meet the following three criteria:

i. All symptoms (nasal congestion, cough, sore throat, headache, fatigue, sleep disturbances) are improved to 'Lack of symptoms' or 'Very mild'. This will only be achieved if the severity each clinical symptom decreases to ≤2 points, without any further deterioration by the end of the study, and an overall score of ≤12 points as determined by the sum of the severity of each symptom. Scores will be based on the VAS taken twice daily (morning and evening) for the duration of the follow-up period.
ii. The axillary temperature has been permanently reduced to <37.0°C (requiring two consecutive measurements at 12 hour interval where the value is <37.0°C), without any further spikes in temperature registered to the end of the follow-up period. The axillary temperature will be taken by the subject twice daily (morning and evening) for the duration of the follow-up period.
iii. The decrease in axillary temperature to <37.0°C has occurred without any antipyretic intake.

Average disease duration: the duration will be defined as the interval between the initiation of treatment till when the subject meets the criteria for "Clinically recovered" in all 3 studies. The severity of each symptoms (headache, fatigue/easy fatigue, sleep disturbances, nasal

congestion, sore throat, cough) will be evaluated by the individual subjects using the VAS as follows: 0 = Lack of symptoms; 2 = Very mild symptoms; 4 = Mild symptoms; 6 = Moderate symptoms; 8 = Severe symptoms, 10 = Very severe; and will be recorded in the subject's diary data. To be considered ''Clinically recovered", the subject must have a score of ≤2 points in each of the symptoms assessed.

Secondary outcome measure

1. *Percentage of patients with lasting axillary temperature below 37.0°C*: such patients will require two consecutive temperature measurements below 37.0°C, without any antipyretic intake, based on data from the patient's diary.
2. *Period required for a persistent decrease in temperature*: this period will be determined at the beginning of the first 24-hour period in which axillary temperature returns to <37.0°C (requiring are two consecutive temperature measurements in which the value is <37.0°C, without any antipyretic intake), based on data from the patient's diary.
3. *Percentage of patients taking antipyretics*: this will be calculated based on YES/NO answer (whether subjects were taking antipyretics or not), based on data from the patient's diary.
4. *The duration of the antipyretic intake*: this will be determined at the beginning of the first 24-hour period in which the patient does not take antipyretics (i.e. two consecutive 12-hour intervals without antipyretic intake), based on data from the patient's diary.
5. *The decrease of clinical symptom severity*: the total mean score of symptoms will be based on the severity of each symptom: headache, fatigue/easy fatigue, sleep disturbances, nasal congestion, sore throat, cough as evaluated by a VAS (0-10) for the symptom severity, based on data from the patient's diary. The minimum score will that of 0, and the maximum score will be that of 60. A reduction of the overall value will be considered as an improvement of the symptoms' severity, whilst a higher score will be considered as worsening of the symptoms' severity. Time range: Since randomization up to the recovery period (Days 1-5/ 1-7), it is measured at every 12-hour intervals.
6. *Number of patients with lasting absence of a particular symptom*: this will be achieved when the symptom in question has improved to 'Lack of symptom' or 'Very mild' (with as VAS of ≤2 points), without any further persistence of the symptom till the end of the studied period, based on data from the patient's diary.

7. *Patients considered to be fully recovered*: This condition evaluation will be performed by each subject at every 12-hour intervals as per scale: ‘Still is feeling ill - 1’, ‘I feel better - 2’, ‘I feel healthy - 3’. To be considered as fully recovered, the subject must choose ‘I feel better’/’I feel healthy’, in two consecutive 12-hour intervals, based on data from the patient's diary.

Eligibility and exclusion criteria

Participant inclusion criteria: Description

1. Both male and female patients, aged 18-60 years for Study 1; aged 13-17 years for Study 2; and aged 5-12 years for study 3
2. Diagnosis of acute upper respiratory tract viral infection: established in terms of axillary temperature > 37,0°C at the moment of examination, and at least one of the symptoms: nasal congestion, sore throat, cough, headache, fatigue/easy fatigue, and sleep disturbance.
3. The first symptom must have presented in preceding 24 hours to GP visit
4. Patient's Informed Consent for study participation signed by the patient in Study 1, or by one parent/guardian in Study 2 and Study 3.

Participant inclusion criteria: Target number of participants

Study 1 – 616 patients

Study 2 – 329 patients

Study 3 – 319 patients

Participant exclusion criteria

1. Inosine acedoben dimepranol or Rimantadine hydrochloride intake.
2. Patients prescribed oseltamivir or zanamivir.
3. Patients with presumed pneumonia, bacterial infection, or severe disease requiring antibacterial agents on the first day of disease.
4. Inclusion of antibiotic in therapy during the duration of the follow-up period.
5. Clinical symptoms of severe influenza/acute upper respiratory tract infection requiring hospitalization.
6. Presumed initial disease symptoms, similar to influenza/acute upper respiratory tract symptoms due to other infectious diseases, flu-like syndrome at the beginning of systemic connective tissue diseases, oncohematological and other diseases.
7. Medical history of primary and secondary immunodeficiencies.
8. Medical history of sarcoidosis.
9. Patients with diabetes or severe chronic heart, liver, kidney or brain disease.

10. Oncological diseases.
11. Exacerbation or decompensation of chronic diseases affecting the ability to participate in the clinical trial.
12. Medical history of polyvalent allergy.
13. Allergy/intolerance to some of ingredients of the tested product used upon the treatment.
14. Malabsorption syndrome, including congenital or acquired lactase or other disaccharide deficits, galactosemia.
15. Drug addiction, consumption of 2 or more alcohol units per day by the patient.
16. Mental disorders of the patient.
17. Patients who according to the researcher's opinion, do not comply with the study requirements or product dosing regimen.
18. Participation in other clinical trials within 3 months prior to study inclusion.

Study Location

Countries of recruitment

Bulgaria

Trial participating centre

85 GP practices

Sponsor contact

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