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NEW ANTIHISTAMINE DRUG IN TREATMENT OF PATIENTS WITH SEASONAL ALLERGIC RHINITIS: CLINICAL STUDY RESULTS

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ABSTRACT
Current prevalence of allergic diseases (AD) stands for a considerable medical and social issue. In the scope of overall morbidity structure, seasonal allergic rhinitis (SAR) is one of the most common AD; according to various estimates, from 10 to 25 % of the population is affected by SAR[1,2]. By itself, SAR is not classified as a serious disease, but its symptoms significantly worsen patient's quality of life and necessitate protracted administration of medications that induce a range of adverse effects. This abstract provides pharmaceutical characteristics and shows findings of the open-label, randomized clinical trial of efficacy and safety (phase III) of a new Teoritin® antiallergenic preparation compared to Aerius® (Desloratadine) reference drug in treatment of 124 patients with SAR. Trial results confirm no less efficacy and comparable safety of Teoritin® drug from the viewpoint of improvement (reduction) of SAR symptoms intensity after 14 days of treatment.

Keywords: Teoritin, seasonal allergic rhinitis, clinical study.
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INTRODUCTION
Antihistamine drugs represent the class of principle means to treat most ADs mediated by Histamine. Antihistamine medications provide for blockade of Histamine effects on H_1-receptors through activation of competitive inhibition mechanism; moreover, their affinity to this type of receptors is significantly lower in comparison with Histamine. Therefore, these drugs cannot displace receptor-bound Histamine, and the activity produced is focused only on blocking of free or vacated receptors. Thus, H_1-receptor antagonists are mostly efficient from the viewpoint of prevention of immediate type allergic reactions, and in the instances of already developed response, these drugs preclude release of new amounts of Histamine.

Despite availability of fairly extensive range of antihistamine drugs used in the medical practice as antiallergenic remedies, the search for new H_1-histamine receptors antagonists remains a pending issue of the agenda, taking into account that most existing drugs of this class possess inherent drawbacks, such as short period of action, development of adverse reactions affecting the Central Nervous System, etc.[3,4].

From this viewpoint, special interest has been focused on the search for original antihistamine (antiallergenic) preparations with innovative chemical structures.

To succeed with this mission, Russian scientists have synthesized and investigated a vast group of 1- and 7-derivatives of Xanthine; the compound with most potent activity was (7-[4-(4-Benzhydrylpiperazinyl-1)Butyl]-3-Methylxanthine Succinate), given the name of Teoritin. The following considerations have been accounted for in course of Teoritin® structure formation:

1. molecule of a new drug should contain Benzhydrylpiperazinyl-Alkyl moiety standing for the principal pharmacophore part of the structure of certain modern antagonists of H_1-histamine receptors, namely, Cetirizine, Meclozine, etc.;
2. with the reference to Benzhydrylpiperazinyl-Alkyl moiety, it has been planned to assign the role of transporter system to biogenic structure of Xanthine that is the basement of some drugs and natural compounds.

One of the main approaches to development of new drugs is still focused on modification of the structure of pharmacologically active substances. In this respect, to produce a new preparation (guided by a package of technological and economic reasons), it has been decided to select rather affordable 3-Methylxanthine as the source compound, which substance is extensively used in the synthesis of many drugs, showing no sedative properties considered adverse for antihistamine preparations[5,6].

Findings of investigation of general pharmacological properties of Teoritin® carried out in the framework of preclinical trials of the compound have demonstrated that if used in the doses corresponding to antihistamine and antiallergenic dose range, the drug does not induce untoward effects on the principal systems and functions of the organism. Central anti-muscarinic action of Teoritin® is observed upon use of doses 3-4-fold higher than those used to induce antihistamine activity. Results of studying central effects of Teoritin® give certainty to conclude that like Cetirizine and in contrast with antihistamine (antiallergenic) drugs of the 1st generation, the drug concerned does not produce any depressing influence on the CNS.

One of possible proposed indications for the clinical use of the new drug has encompassed seasonal allergic rhinitis (SAR), being one of the most prevalent allergic diseases that almost all patient age groups are exposed to.

SAR development mechanism stands for a classic example of immediate type IgE-mediated allergic reaction. The group of main participants involved to the allergic inflammation emerging in the nasal mucosa as result of interaction between allergen and specific IgE-antibodies comprises mast cells, eosinophils, lymphocytes, epithelial and endothelial cells. Allergen-specific IgE-antibodies abundantly produced upon contact with the allergen in the organisms of subjects with predisposition to atopy are fixed on the high-affinity receptors located over mast cells. This process induces

sensibilization of the nasal mucosa. Following contact with the allergen and binding of the latter with IgE-antibodies fixed over mast cells leads to activation of mast cells and triggers secretion of mediators of the allergic inflammatory response, such as Histamine, Tryptase, Kinins, Cysteinyl Leukotrienes (C4, D4, E4) and Prostaglandin D2. Mediators' effects in the endothelial cells of the blood vessels and neuroceptors of the nasal mucosa entail the development of SAR clinical symptoms.

SAR treatment should be focused on reaching and maintenance of control over symptoms of the disease, prophylaxis of this morbidity exacerbations, improvement of patients' quality of life, treatment of the concomitant pathology that aggravates the course of SAR, and prevention of bronchial asthma development.

In the scope of new medicinal product registration, phase I – III clinical studies have been successfully performed; main findings of phase III clinical study are provided below.

MATERIALS AND METHODS

This clinical study has been approved and filed by the Ministry of Healthcare of the Russian Federation; registration No. 270 dated 05th of June 2018 (Clinical Study Protocol TEORITIN-04).

The objective of the clinical study: to assess efficacy and safety of Teoritin® drug (4 mg tablets, manufactured by ZAO Obninsk Chemical Pharmaceutical Company, Russia) as compared to Aerius® drug (5 mg film-coated tablets, manufactured by Schering-Plough Labo N.V., Belgium) in adult patients with seasonal allergic rhinitis.

Study design: multicenter prospective open-label randomized clinical study of efficacy and safety of the drug.

This clinical study has been conducted in compliance with the principles of the Declaration of Helsinki and GCP (Good Clinical Practice) rules. The clinical study Protocol and Informed Consent Form have been reviewed and approved by the Institutional Ethics Committee. The clinical study program included screening phase lasting up to 7 days, 14-days' active therapy period and observation period lasting up to 8 days. Overall clinical study duration for each participating patient has been set below 29 days. The clinical study course has stipulated for conducting 5 visits: screening visit (Visit 1), randomization / treatment commencement visit (Visit 2), interim therapy efficacy assessment visit (Visit 3), therapy termination visit (Visit 4) and end of observation period visit (Visit 5).

126 patients have been screened to participate in this clinical study, of which all 126 patients have been randomized. All patients have been made aware of the objective and nature of the clinical study, and have signed the Informed Consent Forms in agreement to participate.

Main Inclusion Criteria:

1. Presentation of signed Informed Consent Form in agreement to participate in the study;
2. Patients of either sex aged 18 – 65 years with moderate to severe seasonal allergic rhinitis / rhino-conjunctivitis;
3. Minimum 2-years' history of SAR prior to screening visit;
4. Documented positive results of allergic challenges and/or elevated level of specific IgE-antibodies to pollen allergens identified at the blood serum analysis performed in 24 months prior to screening visit;
5. Not less than 6 points scored over reflective Total Nasal Symptom Score for the period of 24 hours (rTNSS), whereas:
   a) minimum 2 points scored for nasal congestion at Visit 2 (randomization);
   b) presence of at least two out of three remaining symptoms (runny nose, itchy nose, sneezing) at Visit 2
6. Negative urine pregnancy test, expressed consent to fully abstain from sexual intercourse or to implement reliable contraception methods for women of child-bearing potential during the entire period of the clinical study.

Main Exclusion Criteria:

1. Negative or dubious result of allergic challenges;
2. Presence of constant symptoms of perennial rhinitis;
3. Patients with the symptoms of perennial rhinitis only or patients with the symptoms of SAR, if in the previous periods such patients demonstrated positive results of skin allergic challenges with application of the allergen not typical for blossom season, in course of which the present clinical study is conducted;
4. Bronchial asthma present for 2 years that necessitated permanent treatment implementation;
5. Patients with other kinds of rhinitis (including rhinitis medicamentosa, atrophic rhinitis);
6. Clinically relevant deformation of nasal cavity;
7. Surgical intervention in 30 days prior to screening visit or traumatic lesion of the nose with incomplete recovery;
8. Local bacterial infections (of acute or chronic type) with involvement of nasal cavity mucosa;
9. Upper respiratory tract infections developed in 30 days prior to screening visit;
10. Active tuberculous process or history of tuberculosis;
11. Any concurrent somatic diseases or medical conditions that in the opinion of the Investigator can complicate interpretation of treatment outcomes, or can render impossible performance of the procedures scheduled for the present clinical study, or pose a threat for the patient, if participation in the clinical study is continued;
12. Patients in need of concomitant therapies implementation stipulating for administration of any drugs listed in Prohibited Concurrent Treatments Section;
13. Hypersensitivity to any ingredients of the study drug / reference drug.

Patients complying with all inclusion criteria and eligible to participation in the clinical study have been randomized to two treatment groups in the ratio of 1:1. Administration of Teoritin® drug (T) in the dose of 4 mg has been indicated as the study (principal) therapy; administration of Aerius® drug (R) in the dose of 5 mg has been indicated as the reference (control) treatment. Patients took both study drugs orally, on a once daily basis for 14 consecutive days.

Subjects have been issued with a specifically designed Patient's Diary to be completed daily, with a view to record clinical signs and symptoms of SAR. Treatment efficacy has been assessed after 1 and 2 weeks of the therapy.

Criteria for Efficacy Assessment

The primary criterion set for the treatment efficacy evaluation was average change of overall assessment of nasal symptoms evaluated for the period of the last 24 hours (by means of rTNSS scale: reflective Total Nasal Symptom Score) performed at Visit 4 (final assessment of the treatment efficacy), as compared to the baseline.

The group of the secondary criteria for efficacy evaluation included the following items:

- average change of overall assessment of nasal symptoms evaluated for the period of the last 24 hours (by means of rTNSS scale: reflective Total Nasal Symptom Score) performed at Visit 3 (interim assessment of the treatment efficacy), as compared to the baseline;
- average change of overall assessment of nasal symptoms evaluated at the fixed time points (by means of iTNSS scale: instantaneous Total Nasal Symptom Score) performed at Visits 3 and 4, as compared to the baseline;
- average change of overall assessment of ocular symptoms evaluated at the fixed time points (by means of iTNNSS scale: instantaneous Total Non-Nasal Symptom Score) performed at Visits 3 and 4, as compared to the baseline;
- average change of overall assessment of ocular symptoms evaluated for the period of the last 24 hours (by means of rTNNSS scale: reflective Total Non-Nasal Symptom Score) performed at Visits 3 and 4, as compared to the baseline;
- frequency of administration of rescue remedies required to alleviate general condition;
- proportion of patients with response to the treatment at Visits 3 and 4, according to the overall assessment of treatment efficacy reported by patients / the Investigator;
- average change of overall quality of life according to MiniRQLQ Questionnaire (Mini Rhino-Conjunctivitis Quality of Life Questionnaire) at Visits 3 and 4, as compared to the baseline.

Scales and Questionnaires Used

TNSS – Total Nasal Symptom Score: defined as the overall score for each of the following nasal symptoms: runny nose, nasal congestion, itchy nose, sneezing. Intensity of each symptom has been assessed by patients according to the following rating scale: 0 – no symptoms; 1 – mild symptoms; 2 – moderate symptoms; 3 – severe symptoms.

Overall assessment of nasal symptoms for the period of the last 24 hours: total score of nasal symptoms intensity in the period of the last 24 hours has been preferably defined at the same time with recording of the results in the Patient's Diary.

Overall assessment of nasal symptoms evaluated at the fixed time points (instantaneous assessment): evaluation of nasal symptoms intensity at the given moment of time has been performed by patients on a twice daily basis (in the morning and in the evening hours, preferably at the same time) with recording of the results in the Patient's Diary.

TNNSS – Total Non-Nasal Symptom Score: defined as the overall score for each of the following ocular symptoms: eye redness, itchy / stinging eyes, watery eyes. Intensity of each symptom has been assessed by patients according to the following rating scale: 0 – no symptoms; 1 – mild symptoms; 2 – moderate symptoms; 3 – severe symptoms.

Overall assessment of ocular symptoms for the period of the last 24 hours: total score of ocular symptoms severity in the period of the last 24 hours has been preferably defined at the same time with recording of the results in the Patient's Diary.

Overall assessment of ocular symptoms evaluated at the fixed time points (instantaneous assessment): evaluation of ocular symptoms intensity at the given moment of time has been performed by patients on a twice daily basis (in the morning and in the evening hours, preferably at the same time) with recording of the results in the Patient's Diary.

Overall assessment of the quality of life according to MiniRQLQ (Mini Rhino-Conjunctivitis Quality of Life Questionnaire)[7] has been defined as the total points scored for each of the following parameters: routine daily activities, practical issues, nasal, ocular and other symptoms. Intensity of each symptom has been assessed by patients according to the following rating scale: 0 – not bothersome; 1 – almost not bothersome; 2 – occasionally bothersome; 3 – slightly bothersome; 4 – somewhat bothersome; 5 – very bothersome; 6 – extremely bothersome.

Baseline has been set at the last instantaneous evaluation of the symptoms recorded in the Patient's Diary prior to Visit 2 (randomization) for iTNSS and iTNNSS scales and two last successive assessments made in the period of 12 hours prior to Visit 2 (randomization) for rTNSS and rTNNSS scales.

Assessment at Visits 3 and 4 has been set at the last instantaneous evaluation of the symptoms recorded in the Patient's Diary prior to Visits 3 and 4 for iTNSS and iTNNSS scales and two last successive assessments made in the period of 12 hours prior to Visits 3 and 4 for rTNSS and rTNNSS scales.

Safety and tolerability of the study drug have been evaluated with respect to the incidence rate and severity of adverse events (AE). All data related to efficacy and safety have been processed by means of NCSS Software Package, version 11.0.

STUDY RESULTS

Statistical analysis of efficacy has been performed in the intention-to-treat (ITT) population (125 subjects: 62 patients in T group (treatment with Teoritin® drug) and 63 patients in R group (treatment with Aerius® drug), and in the per protocol (PP) population (124 subjects: 61 patients in T group and 63 patients in R group).

Background Characteristics

All randomized patients showed total course of the disease in excess of 2 years from the time it has been diagnosed. With the reference to ITT population, average duration of the disease from the time of diagnosis was 6.85 ± 5.22 years in the group of Teoritin® drug administration and 6.70 ± 5.83 years in the group of treatment with Aerius® drug.

All patients have been diagnosed with moderate to severe seasonal allergic rhinitis / rhino-conjunctivitis; severe seasonal allergic rhinitis / rhino-conjunctivitis has been

diagnosed in 2 subjects from T group and in 4 subjects from R group. No statistically significant differences have been established between T and R treatment groups from the viewpoint of the disease severity grade ($p = 0.679$).

In all evaluated populations in the group of Teoritin® drug administration, overall assessment of nasal symptoms intensity for the last 24 hours (as per rTNSS scale) (average value for the total score of 2 last evaluations made in the period of 12 hours) prior to randomization (at the baseline) has varied from 6 to 10 points; similar value in the group of treatment with Aerius® drug ranged from 6 to 11.5 points. No statistically significant differences have been established between T and R treatment groups from the viewpoint of the disease severity grade in the period of the last 24 hours (as per rTNSS scale) ($p > 0.05$).

The groups in both populations have been basically well-balanced with regards to the principal vital signs values and laboratory tests results (complete blood count, blood chemistry and urinalysis).

In pursuance of the clinical study Protocol, the primary criterion set for the treatment efficacy evaluation was average change of overall assessment of nasal symptoms evaluated for the period of the last 24 hours (by means of rTNSS scale) performed at Visit 4, as compared to the baseline, according to the data recorded in the Patient's Diaries. Efficacy analysis has been carried out for the primary endpoint in ITT and PP populations.

Intergroup comparison of average change (Δ) of the total score of nasal symptoms evaluated in the period of the last 24 hours (by means of rTNSS scale) at Visit 4, as compared to the baseline, has not resulted in statistically significant differences between groups of patients treated with T and R medications, in neither population analyzed ($p = 0.725$ for ITT population and $p = 0.688$ for PP population).

Calculated upper limits of 95 % Confidence Interval (CI) for the difference of mean values of the groups of principal (T) and control (R) treatments have reached 0.655 and 0.643 in ITT and PP populations, respectively; the values so computed do not cross the non-inferiority margin of 0.8 (see **Table 1** below) and therefore certifies the no less efficacy of Teoritin® study drug as compared to Aerius® reference drug in regards to average change of the intensity of nasal symptoms at Visit 4, as compared to the baseline.

TABLE 1.comparative analysis of treatment efficacy with respect to the primary efficacy criterion (PP population)

Study drug	Nasal symptoms average intensity score	Difference of nasal symptoms average intensity scores	Upper limit of 95 % CI for the difference of average scores
T	-6.63 ± 1.90	-0.0238	0.643
R	-6.61 ± 1.88		
Student *t*-test for differences of the means, T			

Secondary Criteria for Efficacy Evaluation

Analysis of variance (ANOVA) of repeated measurements has not shown statistically significant differences between patient groups taking T and R drugs ($p > 0.05$) with respect to any of the secondary criteria for efficacy evaluation.

Safety

Adverse Events (AEs)

In course of the present clinical study performance, 192 AEs have been registered (100 AEs in the group of patients treated with Teoritin® study drug, and 92 AEs in the group of patients treated with Aerius® reference drug). On the whole, AEs have been observed in 83 subjects (46 patients in the group of Teoritin® study drug administration and 37 subjects in the group of Aerius® reference drug administration).

Comparison of the number of patients with observed AEs has not shown statistically significant differences between T and R treatment groups ($p = 0.133$; Pearson's chi-squared test). The most prevalent AEs were variations in baseline laboratory tests values (complete blood count, blood chemistry and urinalysis) reported at Visit 4.

Physical Examination Findings; Vital Signs:

Physical examination results have not shown any differences between groups at any of the visits to the study sites. No statistically significant differences have been found between two treatment groups ($p > 0.05$) with respect to the impact of the drugs on vital signs (namely, heart rate, breathing rate, arterial pressure and body temperature).

Complete Blood Count, Blood Chemistry, Urinalysis Values:

According to the test values, both at Visit 1 and at Visit 4, insignificant hematological variations and changes in the urinalysis values have been observed in patients from both treatment groups with similar frequency. The changes so identified have been interpreted as of random and clinically irrelevant nature, according to the Investigators ($p > 0.05$).

ECG:

Electrocardiogram (ECG) results have not shown statistically significant differences between T and R treatment groups ($p > 0.05$).

DISCUSSION AND CONCLUSIONS

SAR represents a heterogeneous and extremely prevalent group of allergic diseases. SAR is capable to produce considerable adverse impact on the quality of life of patients, inducing problems of psychological nature and leading to reduction of working and learning capacity. It has been established that allergic rhinitis is a predisposing factor in regards to development of more serious morbidities that rather often result in patients' disability[8,9]. In about 20 – 40 % of patients allergic rhinitis is later transformed into bronchial asthma. Currently, SAR is considered as a disease that requires significant treatment expenditures. Total costs are defined by direct medical expenses and higher indirect outlays[10]. Findings of multiple clinical trials clearly demonstrate significant economic burden of this disease for

an individual, healthcare system and the whole community [11,12].

International position papers have substantiated the expedience of broad use of 2nd and 3rd generation antihistamine drugs, intranasal Corticosteroids and oral decongestants in treatment of SAR, and proposed a stepped approach towards selection of such remedies. It has been stated that the choice of antiallergenic medications should be made in consideration of their efficacy, cost and, subsequently, affordability for the majority of patients.

New antihistamine drugs stand for the primary agents to treat patients with SAR, and should possess proven higher efficacy in management of symptoms of the disease, as well as good tolerability without sedative effect even though administered in increased doses.

Newly developed antihistamine Teoritin® drug has demonstrated good results in the framework of the clinical study conducted. Upon comparison with an approved and attested reference preparation of Desloratadine (presented as Aerius® drug) it has been shown that analyzed treatment groups were comparable on account of the primary safety parameter, as well as from the viewpoint of secondary efficacy variables.

With the reference to the primary criterion it has been demonstrated that the lower limit of 95 % Confidence Interval (CI) for the difference of mean values of the principal and control groups (ITT population) has reached 0.655; this value does not cross the non-inferiority margin of 0.8 and therefore certifies the no less efficacy of Teoritin® study drug as compared to Aerius® reference drug in regards to reduction of nasal symptoms intensity in subjects with SAR. As for the secondary criteria set for efficacy assessment, this clinical study has also shown the lack of any differences between compared groups.

Results of the analysis performed give grounds to conclude that Teoritin® study drug is safe, as it does not induce appreciable adverse effects, according to investigations of time course laboratory test values and instrumental methods of the study (before and after implementation of therapy course of the drug administration), neither leads to any negative variations affecting organs and systems of the organism, basing on the physical examination findings. Teoritin® study drug has no potential of considerable effects on the vital signs, and is not inferior to the safety profile of Aerius® reference drug.

Therefore, findings of the present clinical study provide grounds to conclude on the no less efficacy of Teoritin® study drug, as compared to Aerius® reference drug from the viewpoint of improvement (reduction) of nasal symptoms intensity in patients with SAR after 14 days of treatment with the drugs concerned.

CONCLUSION

According to the International and domestic position papers, non-sedating antihistamine drugs are recommended as the first line agents of the pharmacological treatment of SAR. New Teoritin® original drug possesses proven efficacy in the scope of SAR symptomatic treatment, along with favorable safety profile. Use of Teoritin® drug in patients with SAR is accompanied with considerable improvement of their quality of life. Findings of the present clinical study provide grounds for rendering recommendation to use the brand new antihistamine Teoritin® drug for treatment of patients suffering from SAR.

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