2. SYNOPSIS

Name of Sponsor Company Daiichi Sankyo Italia ***Name of finished product*** Paspat 3 mg tablets, product already on the market ***Name of active ingredient*** Bacterial lysate containing at least $1X10^9$ germs of the following trains: Staphylococcus aureus, Streptococcus mitis, Streptococcus pyogenes, Streptococcus pneumoniae, Klebsiella pneumoniae, Branhamella catarrhalis, Haemophilus influenza (total:3 mg).	***Individual Study Table referring to the dossier*** PART: [……] VOLUME: [……] PAGE: [……]	***(for National Authority use only)***

Title of the study

ACASP (ADULT CLINICAL ASSESSMENT STUDY ON PASPAT) - RANDOMIZED, PROSPECTIVE DOUBLE-BLIND PLACEBO CONTROLLED STUDY FOR THE EVALUATION OF THE NUMBER, DURATION AND SEVERITY OF RESPIRATORY TRACT INFECTIONS IN ADULTS WITH RISK OF RECURRENCE AFTER STANDARD TREATMENT WITH BACTERIAL LYSATES PASPAT 3 MG TABLETS, OVER AN OBSERVATION PERIOD OF SIX MONTHS.

Principal Investigators/National coordinators:

The study was conducted in Italy, by involving 25 Italian General Practitioners geographically distributed in three Italian health districts. Dr Leonardo Piselli (USL Umbria 2, Spoleto, PG) acted as national study coordinator.

Publication (reference) Unpublished to date (February 2019)	***Clinical phase*** Phase 3 (confirmatory study requested by AIFA)
Date of first enrolment 16 September 2016 (first randomized patient)	***Date of last completed*** 02 August 2018 (last visit of the last patient)

Objectives

Primary objective

To assess the clinical efficacy of Paspat 3 mg tablets in preventing, number and severity of recurring infections of the respiratory tract in adults at risk, testified by at least six recurrences in the previous 12 months.

Secondary objective

To compare, active and placebo groups, the duration of RTI (LRTI and URTI) in adults.
To evaluate the consequences of RTI (LRTI and URTI) on loss of working or school days, hospitalization and use of other treatments.
To document the safety of Paspat 3 mg tablets.

Study design

This Phase 3 trial was conducted as a national (Italian), multicenter, double-blind, placebo-controlled, two arms, parallel groups trial on 211 randomized patients suffering from more RTI (LRTI or URTI) than expected for age.

Patients with at least 6 medically documented RTI (LRTI or URTI) episodes, with a maximum of 18 in the 12 months prior recruitment, were randomized into one of the following treatment groups: Paspat 3 mg tablets (bacterial lysates) or placebo. Randomization did not take place before September 2016 in order to start the study treatment during the Fall period. At the end of about 12 weeks double-blind treatment period, patients were followed up for another about 6-month period in order to evaluate recurrences of RTI (LRTI or URTI) episodes.

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Patient population

Paspat 3 mg tablets is indicated in the prophylaxis of RTI (LRTI and URTI) in adults with medical history of recurrent episodes. The population under study was selected according to this approved indication and consisted of adults aged 18-80 years old at randomization visit.

Main inclusion criteria

Patients with all the following criteria were eligible for inclusion in the study protocol:
1. Male or female.
2. Aged 18 to 80 years achieved.
3. Patients with at least 6 RTI (LRTI or URTI) episodes confirmed by medical recording or patient's reported history, with a maximum of 18, during the 12 months prior randomization.
4. Patient's written consent for participation in the study.
5. Possibility for the study's GP, to have regular telephone contacts with patient.
6. Patients who were supposed to be cooperative with regard to compliance with study-related constraints.

Main Exclusion Criteria

Patients were not eligible for the clinical investigation if they met one or more of the exclusion criteria listed below:
1. Women with childbearing potential not using effective contraception (oral contraceptives, intrauterine device, tubal ligation or other efficient procedures).
2. Women referring, at the screening visit, to be pregnant or breast feeding or women likely to become pregnant during the time of the study.
3. Previous major surgery in the oral, nasal or respiratory tracts (except tonsillectomy or adenectomy) like: cleft lip, palate, nasal surgeries etc. or anatomical damage to the respiratory tracts due to intubation.
4. Anatomic abnormalities of oral, nasal or respiratory tracts.
5. Fever at the time of randomization.
6. Known allergic rhinitis from patient's medical history/records not controlled by standard therapy.
7. Acute broncho-pulmonary infection (bronchiolitis, pneumonia, tuberculosis) at the time of randomization.
8. Chronic broncho-pulmonary disorders such as active asthma needing systemic use of steroids (e.g. oral, intramuscular or intravenous) or bronchiectasis treated with corticosteroids.
9. Oral, nasal or respiratory abscess, including also chronic suppurative otitis media.
10. Cystic fibrosis, primary abnormalities of mucociliary clearance (for example Kartagener's syndrome).
11. Known α-1 anti-trypsin deficiency from patient's medical history/records.
12. Auto-immune disease (e.g. nephropathy, insulin-dependent diabetes mellitus, rheumatoid purpura, juvenile idiopathic arthritis).
13. Acute intestinal infections.
14. Severe systemic diseases, including Human Immunodeficiency Virus (HIV) infection, severe haematological diseases, cancer and otherwise severely compromised patients.
15. Medical history of hypersensitivity to Paspat 3 mg tablets or any drug excipients.
16. Any on-going specific or non-specific immunotherapy with pharmacological effects on the immune system (including homeopathic or phytotherapy) whatever route of administration, 3 months prior to inclusion and/or planned during the course of the study, except regular vaccinations.

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17. Any homeopathic or phytotherapy treatment used for preventing recurrent infections or for improving immunity in the 3 months prior randomization.
18. Participation in another interventional clinical trial at the time of the randomization or within 4 weeks before randomization.
19. Patient's or family's difficulties or problems, in the judgment of the investigator, in being compliant with study procedures and requirements, including social or mental constrains.

Test product, dose and mode of administration, batch number

	Paspat	**Placebo**
Dosage	3 mg	3 mg
Duration of the therapy	**a)** First treatment period of 28 days b) Off-drug period of 28 days c) Second treatment period of 28 days	a) First treatment period of 28 days c) Off-drug period of 28 days c) Second treatment period of 28 days
Mode of administration	Oral (whole tablet, away from meals)	Oral (whole tablet, away from meals)
Lot number	A16/004K	A16/004K

Statistical methods

Different analysis sets were defined in the clinical study protocol and patients to be included in each set were selected on the basis of major protocol violation in the "Blind review document " (Final version: October 15th, 2018).

All sets were identified and finalized before the database lock. The Full Analysis Set (FAS) included all randomized patients having received at least one dose of the study treatment. The Per Protocol (PP) set included the subset of the Full Analysis Set composed of all patients without any major protocol deviation or other source of bias for primary criteria analyses and characterized by a treatment compliance $\geqslant$50%, evaluations of RTI (LRTI and URTI) in the 6 months follow-up and no premature withdrawal after completion of the treatment period.

Quantitative parameters were summarized using descriptive statistics: number of cases (or patients), mean, standard deviation, median and range. Qualitative parameters were summarized using frequency tables: number of cases (or patients) and percent of categorical class (%). If needed or appropriate, treatment groups were compared as regards patient's sex, by means of Chi-square test, and age, by means of Student's t-test.

As regards primary endpoint, comparison between Paspat 3mg and placebo was performed by using an Analysis of Covariance (ANCOVA) with treatment as main factor, and age, sex, number of episodes occurred in the past and use of inhaled corticosteroids/bronchodilators as covariates.

All statistical tests were carried out at a significant level (α level) of 0.05, two tailed.

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SUMMARY

Study population

Full randomized set included 211 patients: 105 (49.8%) in the Paspat group, 106 (50.2%) in the placebo group. Full Analysis Set (FAS) included all randomized patients having received at least one dose of the study treatment (N=208): 102 (49.0%) in the Paspat group and 106 (51.0%) in the placebo group. Per Protocol (N=203) set was a subset of the Full Analysis Set and consisted of all patients without any major protocol deviation.

Out of 208 subjects, 90 (43.3%) were males and 118 (56.7%) females, all but one were of Caucasian ethnic origin (99.5%) and the age ranged from 18.2 to 80.9 years. More than three quarters of patients were non-smoking (77.9%). The remaining (22.1%) declared to be smoker from at least two up to fifty years.

In the 12 months prior randomization, patients reported 7.3 ± 1.37 episodes of recurring respiratory infections, ranging from 6 to 15 events. Overall, findings from baseline medical history, physical examination, concurrent illnesses, previous vaccinations and concomitant medications were well matched in the two study groups.

Efficacy

During the 3-months treatment period, a total 179 RTI occurred in 118 patients (57.0% of FAS), 87 events in 58 patients treated with Paspat (mean 1.50 episodes per patient) and 92 in 60 patients assuming placebo (mean 1.53 episodes per patient).

By considering the primary endpoint, that is the number of episodes of RTI (URTI and LRTI) over the 6 months of the observation period, results from FAS and PP set overlap.

A total 207 episodes occurred in 105 patients (51.7% of PP), 104 events in 50 patients treated with Paspat and 103 in 55 patients assuming placebo. By considering all 203 patients having completed the 6 months of the observation period, the mean number of episodes (LRTI + URTI) was 1.02 ± 1.30, ranging from 0 to 6. Episodes had a mean duration of 6.07 ± 3.90 days, lasting from 2 to 28 days.

Paspat and placebo groups showed similar values (respectively 1.03 ± 1.39 episodes with duration from 2 to 28 days, and 1.01 ± 1.21 episodes with duration from 2 to 22 days). No statistically significant difference between groups was revealed by comparing the total number of episodes ($p = 0.7751$).

A total of 27 patients declared absences from work or school due to the episodes. Absences occurred in 8 patients (7.9%) in the Paspat group and 19 (18.6%) in the placebo group ($p = 0.023$, chi-square test). The mean duration of the absences was 5.25 ± 2.73 and 5.12 ± 4.67 days in Paspat and placebo groups respectively

Regarding markers to assess severity of the episodes (use of NSAIDs, antibiotics and corticosteroids), in total 33 patients assumed NSAIDs: 12 (11.9%) and 21 (20.6%) in the Paspat and placebo group respectively ($p = 0.093$, chi-square test), 56 patients assumed antibiotics: 26 in the Paspat (25.7%) and 30 in the placebo group (29.4%), and 25 patients were treated with corticosteroids: 11 (10.9%) in the Paspat group versus 14 (13.7%) in the placebo. One RTI complication (asthmatic episode) was recorded in a patient treated with Paspat vs 7 complications in the placebo group. Moreover, one patient assuming placebo was hospitalized for 7 days.

Safety

During the study period 209 (45.6%) AEs were reported in the Paspat group and 249 (54.4%) in patients assuming placebo. Six out of there 458 AEs were reported as SAEs, 3 per group, all of them not related to the study drug. About the half of the AEs were mild and the remaining 50.9% was reported as moderate or severe in

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grade, with the same profile in the two study groups. Eleven AEs (2.4%) were related to the study drug (8 in the placebo group and 3 for patients assuming Paspat). Seven of them occurred during the dosing period: 2 (flatulence and URTI) in two patients assuming Paspat and 5 (abdominal pain, headache, dysmenorrhea, pruritus and rush) in three patients assuming placebo. In addition, 3 AEs possibly related with study drug were reported, all from patients assuming placebo. Most of the AEs in both groups needed corrective treatment: 81.1% in the placebo group and 83.3% in the Paspat one. About 90% of the AEs resolved during the study period, with identical pattern in the two groups.

One episode of tachyarrhythmia determined the death of a patient assuming placebo. It occurred in a 78 year-old male suffering from type 2 diabetes mellitus, atrial fibrillation, chronic obstructive pulmonary disease, hypertension, and dyslipidemia, was considered by the investigator not related to the treatment under study.

No relevant finding emerged at the physical examination and for body weight in both groups, either during the dosing period and during the following 6-months follow-up period.

Conclusions and discussion

Overall, Paspat showed a safety profile not distinguishable from placebo, both during the 3-months dosing period and during the next 6-months follow-up period. The results of this study confirm the findings from previous studies on Paspat and post-marketing safety data, in general.

Regarding the primary end-point this study did not demonstrate benefit of Paspat over placebo in preventing recurrence of RTIs during a 6-months observation period, at least in the part of the year ranging from late Autumn to early Summer, with the vast majority of patients observed during the Spring.

Regarding the secondary end-points, the study suggested that Paspat is able to reduce the number of absences from work or school, the consumption of NSAIDs (about 8% vs placebo), antibiotics (about 4% vs placebo) and corticosteroids (about 3% vs placebo) and the RTI complications (1 vs 7 in the FAS).

However, the larger part of the observation periods occurred in Spring 2017 or in Spring 2018 and 88.7% of the patients were observed for the half of the time in there periods. In Italy, Spring 2017 was the 2nd hottest Spring since year 1800, whereas 2018 was, up to September, the hottest never recorded since year 1800, with mean outdoor temperatures up to 3°C and more, over the seasonal references.

Epidemiological evidences indicate that an increase of about 3°C is able to determine a decrease of nearly 50% of the incidence of influenza "like" illness" episodes. The opposite trend is observed when the temperature decreases.

As a difference of only 0.8 RTI episodes between Paspat and placebo was set as primary end-point of this study, there are reasonable arguments to suspect that the huge diminution of the acute RTI episodes during the 6-months follow-up period, paid a crucial role in determining the lack of differences between Paspat and placebo. However, when the few episodes occurred, Paspat was able to assure a minor severity compared to placebo.

In conclusion, this study confirmed the safety of Paspat at the recommended dispensing regimen. Despite this study shows signals suggesting the benefit of the immunization with Paspat, unpredictable and extreme external environmental conditions does not allow to confirm or to reject the assumption that Paspat can effectively prevent recurrence of RTIs in adults.

Date of the report

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