



## Clinical trial results:

**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 Paspas 3 mg tablets, over an observation period of six months.**

## Summary

EudraCT number	2016-000978-38
Trial protocol	IT
Global end of trial date	02 August 2018

## Results information

Result version number	v1 (current)
This version publication date	26 July 2021
First version publication date	26 July 2021
Summary attachment (see zip file)	Prot. DS IT-2015-01 SUMMARY of RESULTS (Prot. DS IT-2015-01 SUMMARY of RESULTS.pdf)

## Trial information

### Trial identification

Sponsor protocol code	DSIT-2015-01
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### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

## Sponsors

Sponsor organisation name	Daiichi Sankyo Italia S.p.A
Sponsor organisation address	Via Paolo di Tono, 73, Roma, Italy,
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Notes:

## Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 August 2018
Global end of trial reached?	Yes
Global end of trial date	02 August 2018
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

After the finalization of Vers. 1.0 of the protocol (18 Apr 2016), three substantial amendments were generated: Vers. 1.1 embedding substantial amendment 20 Sep 2016, Vers. 1.2 embedding substantial amendment 27 Oct 2016 and Vers. 1.3 embedding substantial amendment 16 Nov 2016. Regulatory procedures including IEC/CA submission were carried out by the CRO through the on-line Regulatory Platform (OsSC) set by AIFA.

Having obtained the favourable opinion from the competent ECs, CEC (on 16 June 2016) and following the approval of the Competent Authority (CA) on 06 Jul 2016, sites were initiated

This study (Study identification: DS IT-2015-01; EudraCT Number: 2016-000978-38) was conducted in compliance with specific regulatory requirements of the Italian Ministry of Health, including D.lgs 24 June 2003 no. 211, DPR 21 September 2001 no. 439, DM 26 April 2002, DM 21 December 2007, DM 13 September 2012, Determina AIFA 07 January 2013, Determina AIFA 809/2015.

This trial was conducted in compliance with the most recent version of the Declaration of Helsinki (Fortaleza, Brazil, October 2013), the most recent version of the Good Clinical Practice (GCP), and all applicable regulatory requirements (European Directive 2001/20/EC, 04 April 2001), and Italian Laws (D.lgs no. 211, 24 June 2003 and all applicable regulations).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 September 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 211
Worldwide total number of subjects	211
EEA total number of subjects	211

Notes:

<b>Subjects enrolled per age group</b>	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	206
From 65 to 84 years	5
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted in Italy, by involving 25 Italian General Practitioners geographically distributed in three Italian Districts for Health (ASL), ASL 3 Genovese, ASL1 Imperiese and USL Umbria2. The recruitment was fractionated in two consecutive campaigns, one from 17/09/2016 to 31/01/2017 and the other one from 05/09/2017 to 18/01/2018.

### Pre-assignment

Screening details:

In total 211 patients were screened and randomized by 25 GPs who enrolled an average of 8.4 patients each. A pre-screening was conducted by each GP by querying its own patients' database. All the patients accepted to sign the Informed Consent Form before to be recruited and therefore no screening failure occurred.

### Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	paspap

Arm description:

3 mg tablets

a) First treatment period of 28 days

b) Off-drug period of 28 days

c) Second treatment period of 28 days

Arm type	Experimental
Investigational medicinal product name	PASPAT
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

3 mg/ daily- whole tablet, away from meals

<b>Arm title</b>	placebo
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Arm description:

3mg tablet

a) First treatment period of 28 days

b) Off-drug period of 28 days

c) Second treatment period of 28 days

Arm type	Placebo
Investigational medicinal product name	PLACEBO
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

3 mg/ daily- whole tablet, away from meals

<b>Number of subjects in period 1</b>	paspat	placebo
Started	105	106
Completed	101	102
Not completed	4	4
Adverse event, non-fatal	-	2
Subject's decision	3	2
Exclusion criteria violation	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	overall trial
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Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	211	211	
Age categorical			
Out of 208 subjects in FAS, 90 (43.3%) were males and 118 (56.7%) females that were slightly unbalanced in the two groups (51.0% females in Paspas vs 62.3% in placebo group; the age ranged from 18.2 to 80.9 years well balanced between groups			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	206	206	
From 65-84 years	5	5	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	120	120	
Male	91	91	

## End points

### End points reporting groups

Reporting group title	paspat
Reporting group description:	
3 mg tablets	
a) First treatment period of 28 days	
b) Off-drug period of 28 days	
c) Second treatment period of 28 days	
Reporting group title	placebo
Reporting group description:	
3mg tablet	
a) First treatment period of 28 days	
b) Off-drug period of 28 days	
c) Second treatment period of 28 days	

### Primary: efficacy endpoint

End point title	efficacy endpoint
End point description:	
End point type	Primary
End point timeframe:	
over the 6 months of the observation period	

End point values	paspat	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101	102		
Units: number of episodes RTIs (LRTI + URTI)	104	103		

### Statistical analyses

Statistical analysis title	mean of number of episodes RTI (LRTI+URTI)
Comparison groups	paspat v placebo
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority <sup>[1]</sup>
P-value	= 0.77551
Method	ANCOVA

Notes:

[1] - By considering 203 patients who completed the 6 months of the observation period, the mean number of episodes (LRTI + URTI) was  $1.02 \pm 1.30$ , ranging from 0 to 6. Paspat and placebo groups showed similar values (respectively  $1.03 \pm 1.39$  episodes with duration from 2 to 28 days, and  $1.01 \pm 1.21$  episodes with duration from 2 to 22 days). No statistically significant difference between groups was revealed by comparing the total number of episodes ( $p = 0.7751$ ).

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

overall

Adverse event reporting additional description:

During the study period, 458 AEs were recorded: 209 (45.63%) in the Paspat group and 249 (54.36%) in placebo group. 6 out of 458 AEs were reported as SAE, none of them related to the study drug. Regarding the severity, 225 were considered mild, whereas the remaining 233 (50.9%) were reported as moderate or severe. The severity profile resulted equal to 2 group

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23
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### Reporting groups

Reporting group title	summary AE
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Reporting group description:

206 (98.6%) AEs occurred in the Paspat group were considered unlikely related or not related to the study drug. In the placebo group a total of 238 (95.6%) AEs were reported as unlikely related or not related to the treatment. Eleven AEs (2.4%) were considered related to the study drug (8 in the placebo group and 3 for patients assuming Paspat). Seven of them occurred during the treatment period (TEAEs): two in 2 patients assuming Paspat (flatulence and URTI) and 5 TEAEs in 3 patients assuming placebo (abdominal pain, headache, dysmenorrhoea, pruritus and one rash). 3 AEs possibly related with study drug were reported, all from patients assuming placebo. No AE that occurred in the Paspat group determined the discontinuation of the study drug, whereas in the placebo group one event caused a temporarily discontinuation and another one resulted in a definitely discontinuation of the study drug. Both events were URTI infections.

Serious adverse events	summary AE		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 208 (2.88%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer recurrent			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			



Tachyarrhythmia			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pilonidal cyst			
subjects affected / exposed	1 / 208 (0.48%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	summary AE		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	153 / 208 (73.56%)		
Nervous system disorders			
Nervous system disorders overall	Additional description: including: Cervicobrachial syndrome Headache Migraine Neuralgia Neuritis Paraesthesia Somnolence		
subjects affected / exposed	20 / 208 (9.62%)		
occurrences (all)	23		
Gastrointestinal disorders			
all gastrointestinal disorders	Additional description: including: Abdominal pain Abdominal pain lower Abdominal pain upper Constipation Dyspepsia Enteritis Enterocolitis Flatulence Gastroenteritis Gastroenteritis viral		

subjects affected / exposed occurrences (all)	Gastrooesophageal reflux disease Haemorrhoids Hyperchlorhydria		
	32 / 208 (15.38%) 39		
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders overall	Additional description: Catarrh, Chronic obstructive pulmonary disease, Cough, Dyspnoea, Lower respiratory tract infection, Oropharyngeal pain, Pharyngitis, Pneumonitis, Productive cough, Respiratory tract infection, Rhinorrhoea, Throat irritation, Upper respiratory tract infection		
subjects affected / exposed occurrences (all)	117 / 208 (56.25%) 148		
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders general	Additional description: including: Arthralgia Back pain Incomplete spinal fusion Musculoskeletal chest pain, Musculoskeletal pain Neck Osteoarthritis , Osteoporosis , Pain in extremity , Sciatica Spinal osteoarthritis Spinal pain Tendonitis		
subjects affected / exposed occurrences (all)	33 / 208 (15.87%) 38		
Infections and infestations			
Infections and infestations general	Additional description: Acarodermatitis, Conjunctivitis, Cystitis, Diverticulitis, Dysentery, Epididymitis, Folliculitis, Fungal skin infection, Helicobacter infection, Infected bite, Otitis externa, Otitis media, Pilonidal cyst Rhinitis Tracheiti, Urinary tract, Viral & skin infections		
subjects affected / exposed occurrences (all)	25 / 208 (12.02%) 27		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 November 2016	<p>The CTP was reviewed with 3 SAs: 1)CTP v.1.1,16/04/2016:-Changes of exclusion criterion N.#8: the exclusion of chronic use of corticosteroids has been restricted only to the systemic administration.In fact, inhaled corticosteroids andbronchodilators are necessary for the management of recurrences of Chronic ObstructivePulmonary Diseases and, on the other hand, there is no clinical evidence that temporarily use of inhaled corticosteroids and bronchodilators have effects on thesystemic immune response.-Changes of exclusion criterion N.#17: it has been corrected a discrepancy (6 months instead of 3 months) in the wash-out from any previous treatment active on the immune system; -Changes of exclusion criterion N.#18: it has been clarified that the exclusion from participation in another studies at the time of the randomization or within 4 weeks before, was only restricted to interventional studies.2)CTP v. 1.2,26/10/2016:In reference to the protocol version 1.1, the NCA raised some objections. The CA questioned if the combined use of an effective inhaled anti-inflammatory and/or bronchodilator regimen and the immuno-modulating oral bacterial lysates might lead to an additive or even better protection against COPD. In particular, the protocol has been updated with the following substantial changes:1)in the efficacy analysis the use of inhaled corticosteroids or bronchodilators has been included as covariate;2)regarding one of the Secondary Criteria - insurgence of asthma -, in the efficacy supportive analysis has been specified how the concomitant use of Paspal 3mg tablets and inhaled corticosteroids or bronchodilators would be evaluated for the possible impact on efficacy results;3)CTP v.1.3: the subgroup analyses of the patient affected by asthma and needing treatment of inhaled corticosteroids had to be performed in compliance with EMA rules guidelines.</p>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported