Clinical trial results:
Randomized, prospective double-blind placebo controlled study for the evaluation of the number, duration and severity of Upper Respiratory Tract Infections in children with risk of recurrence after standard treatment with bacterial lysates Paspat 3 mg tablets, over an observation period of six months.

Summary

EudraCT number	2016-000979-24
Trial protocol	IT
Global end of trial date	05 January 2020

Results information

Result version number	v1 (current)
This version publication date	28 June 2023
First version publication date	28 June 2023

Trial information

Trial identification

Sponsor protocol code	DSIT-2015-02

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo Italia SpA
Sponsor organisation address	Via Paolo di Dono, 73, Roma, Italy,
Public contact	Dott. Fabio Romeo,Medical Director, Daiichi Sankyo Italia SpA, +39 0685255, fabio.romeo@daiichi-sankyo.it
Scientific contact	Dott. Fabio Romeo,Medical Director, Daiichi Sankyo Italia SpA, +39 0685255, fabio.romeo@daiichi-sankyo.it

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 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 December 2019
Global end of trial reached?	Yes
Global end of trial date	05 January 2020
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 upper respiratory tract in children at risk, testified by at least six recurrences in the previous 12 months

Protection of trial subjects:

The only versione 1.0 of the protocol (18 Apr 2016), was generated, approved and in force in all sites. 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 21June2016) and following the approval of the Competent Authority (CA) on 06Jul2016, sites were initiated
This study 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 December2007, 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	01 September 2017
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: 178
Worldwide total number of subjects	178
EEA total number of subjects	178

Notes:

Subjects enrolled per age group

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)	178
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in Italy, by involving 4 Italian pediatric hospitals and 2 Italian health districts that involved 23 Italian Pediatricians. Dr. Oliviero Sacco (IRCCS Istituto Giannina Gaslini, Genova) acted as national study coordinator. The recruitment was fractionated in two consecutive campaigns (01/09/2017-12/02/2018 and 01/03/2019)

Pre-assignment

Screening details:

The first patient of the first campaign was randomized on 01 September 2017 and the last one on 12 February 2018, when 119 patients, 57.1% of the planned target, were enrolled. The second wave started on 01 September 2018 and the recruitment continued until 31 March 2019.

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, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	paspat

Arm description:

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

Arm title	placebo

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

Number of subjects in period 1[1]	paspat	placebo
Started	84	89
Completed	75	86
Not completed	9	3
Physician decision	1	-
Subject's decision	2	1
Lost to follow-up	1	-
various reasons	5	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The 178 screened patients were allocated to the treatment groups as follows: 84 received Paspat and 89 received placebo. Four patients allocated in the Paspat group (4.5%) and one in the placebo group (1.1%) did not take any treatment were excluded from FAS analysis that consists of 173 subjects.

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	173	173	
Age categorical			
Out of 173 subjects in FAS, 94 (54.3%) were males and 79 (45.7%) females that were slightly unbalanced in the two groups (52.4% females in Paspat vs 39.4% in placebo group). All but three patients were of Caucasian ethnic origin (96.5%). The age was ranged from 2.6 to 7.0 years, well balanced between groups, with means of 5.0 (± 0.8) and 5.1 (± 0.8) in the Paspat and placebo groups, respectively.			
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)	173	173	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	79	79	
Male	94	94	

End points

End points reporting groups

Reporting group title	paspat
Reporting group description:	
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

End point title	efficacy
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	79	87		
Units: number of episodes URTIs				
number (not applicable)	49	55		

Statistical analyses

Statistical analysis title	mean of number of episodes URTIs
Comparison groups	paspat v placebo
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.94
Method	ANCOVA

Notes:

[1] - Regarding the primary endpoint in the FAS population, 104 patients (62.7%) out of 166 completing 6-months observation period had no episode of URTI, 49 out of 79 in the Paspat group (62.0%) and 55 out of 87 in the placebo group (63.2%). Details shown in Table XVII (Chi square test p = 0.94).

Adverse events

Adverse events information	
Timeframe for reporting adverse events: overall	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23

Reporting groups	
Reporting group title	summary AE

Reporting group description:

During the study period, 676 AEs were recorded in 119 patients: 329 AEs (48.7%) in 63 patients in the Paspat group and 347 AEs (51.3%) in 56 assuming placebo.
Analysing all AEs, only one out of 675 AEs was reported as serious adverse event (SAE) in the placebo group and not related to the study drug.
A total of 524 (79.0%) AEs were considered mild, 73.2% in the Paspat group and 84.4% in the placebo group. Moderate AEs were found in 84 (25.5%) vs 53 (15.2%) patients in Paspat and placebo group respectively. Four severe AEs (1.2%) were all reported in the Paspat group.
No AE was considered related to the treatment in both groups. Two AEs (0.6%), 2 episodes of diarrhoea in the same patient in the Paspat group, were considered possibly related and 2 AEs in each group were considered unlikely related to the treatment. The vast majority of the AEs 324 (98.5%) and 344 (99.1) in the Paspat and placebo group respectively, was not considered treatment related.

Serious adverse events	summary AE		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 119 (0.84%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Adenotonsillectomy			
subjects affected / exposed	1 / 119 (0.84%)		
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 %

Non-serious adverse events	summary AE		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	119 / 119 (100.00%)		
Vascular disorders			

Vascular disorders	Additional description: Haematoma		
subjects affected / exposed	1 / 119 (0.84%)		
occurrences (all)	1		
General disorders and administration site conditions			
General disorders and administrations			
subjects affected / exposed	23 / 119 (19.33%)		
occurrences (all)	23		
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastin	Additional description: Asthma Bronchitis Bronchospasm Cough Epistaxis Influenza Irregular breathing Laryngitis Nasal congestion Nasal obstruction Nasopharyngitis Oropharyngeal pain Pharyngitis Pharyngitis streptococcal Pharyngotonsillitis Pneumo		
subjects affected / exposed	115 / 119 (96.64%)		
occurrences (all)	333		
Injury, poisoning and procedural complications			
Injury, poisoning and procedural	Additional description: Joint injury Tympanic membrane perforation		
subjects affected / exposed	2 / 119 (1.68%)		
occurrences (all)	2		
Nervous system disorders			
Nervous system disorders	Additional description: Headache		
subjects affected / exposed	2 / 119 (1.68%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Blood and lymphatic system disorders	Additional description: Lymphadenitis Lymphadenopathy		
subjects affected / exposed	2 / 119 (1.68%)		
occurrences (all)	12		
Ear and labyrinth disorders			
Ear and labyrinth disorders	Additional description: Ear infection, Ear pain, Otitis media,Otitis media acute, Tympanic membrane hyperaemia		
subjects affected / exposed	36 / 119 (30.25%)		
occurrences (all)	44		
Eye disorders			

Eye disorders	Additional description: Conjunctivitis		
subjects affected / exposed	1 / 119 (0.84%)		
occurrences (all)	1		
Gastrointestinal disorders			
Gastrointestinal disorders	Additional description: Abdominal pain Dental caries Diarrhoea Dysphagia Gastroenteritis Nausea Vomiting		
subjects affected / exposed	25 / 119 (21.01%)		
occurrences (all)	30		
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disease	Additional description: Dermatitis Skin lesion Urticaria Varicella		
subjects affected / exposed	9 / 119 (7.56%)		
occurrences (all)	10		
Renal and urinary disorders			
Renal and urinary disorders	Additional description: Cystitis Dysuria		
subjects affected / exposed	3 / 119 (2.52%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissues	Additional description: Arthralgia Musculoskeletal discomfort Synovitis		
subjects affected / exposed	3 / 119 (2.52%)		
occurrences (all)	3		
Infections and infestations			
Infections and infestations	Additional description: Enterobiasis Infectious mononucleosis Localised infection		
subjects affected / exposed	4 / 119 (3.36%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported