Clinical trial results:
Clinical trial of the efficacy and tolerability of an immunostimulant drug, composed by ribosomal fractions, in socialized paediatric patients in order to prevent recurrent respiratory infections. A randomized, double-blind vs. placebo, multicentre study.

Summary

EudraCT number	2008-000487-17
Trial protocol	IT
Global end of trial date	14 December 2009

Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019

Trial information

Trial identification

Sponsor protocol code	LF-PF-1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pierre Fabre Pharma
Sponsor organisation address	Via GG Winckelmann, 1, Milano, Italy, 20146
Public contact	Dr Sergio Marcassa, Pierre Fabre Pharma, +33 534506169, contact_essais_cliniques@pierre-fabre.com
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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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 December 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 December 2009
Global end of trial reached?	Yes
Global end of trial date	14 December 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluation after 6 months of the effects, vs placebo, of the treatment with Biomunil / Immucytal administrated at the dosage described in the SPC, on the overall duration of the infective episodes.

Protection of trial subjects:

The study has been carried on in agreement with the last version of the Helsinki Declaration, with the applicable regulatory requirements (European Directive 2001/20/EC, 4 April 2001) with the current Italian Laws (DL. Vo No. 211, 24 Jun 2003 and relate legislation) with the good clinical practice (GCP) norms and with the Guidelines ICH on the Clinic experimentation in Pediatrics.

Background therapy:

No information specified

Evidence for comparator:

Immunostimulant action products (ATC J07AX) represent a category extremely heterogeneous of drugs hardly or at all comparable with each other. For such reason, without any exception, all the controlled studies that use these products also use a placebo group.

Actual start date of recruitment	25 August 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 164
Worldwide total number of subjects	164
EEA total number of subjects	164

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	0

months)	
Children (2-11 years)	164
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:

164 paediatric patients between 2 and 5 years of age have been recruited in a period between the second half of august and the second half of December 2008 in 4 centres in Italy.

Pre-assignment

Screening details:

The patients have been screened and randomized into the study the same day (day O).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Immucytal/Biomunil group

Arm description:

84 children were randomised in the experimental group.

Arm type	Experimental
Investigational medicinal product name	Immucytal/Biomunil
Investigational medicinal product code	J022X
Other name	
Pharmaceutical forms	Granules for oral solution
Routes of administration	Oral use

Dosage and administration details:

Flare treatment: One sachet in the morning and fasting for 4 consecutive days per week for three consecutive weeks.
Maintenance treatment: One sachet in the morning and fasting for 4 consecutive days at month. The first administration of the first month of maintenance had to be done exactly one month after the first administration of attack therapy. Consequently each first administration of the following months had to be carried out one month after the first month of administration.
The contents of the sachet had to be dispersed in half a glass of water.

Arm title	Placebo group

Arm description:

80 children were randomised in the placebo group.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules in sachet
Routes of administration	Oral use

Dosage and administration details:

Flare treatment: One sachet in the morning and fasting for 4 consecutive days per week for three consecutive weeks.
Maintenance treatment: One sachet in the morning and fasting for 4 consecutive days at month. The first administration of the first month of maintenance had to be done exactly one month after the first administration of attack therapy. Consequently each first administration of the following months had to be carried out one month after the first month of administration.
The contents of the sachet had to be dispersed in half a glass of water.

Number of subjects in period 1	Immucytal/Biomunil group	Placebo group
Started	84	80
Completed	80	76
Not completed	4	4
Other	2	2
Lack of collaboration	1	2
Request of the parent/guardian	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Immucytal/Biomunil group
Reporting group description:	
84 children were randomised in the experimental group.	
Reporting group title	Placebo group
Reporting group description:	
80 children were randomised in the placebo group.	

Reporting group values	Immucytal/Biomunil group	Placebo group	Total
Number of subjects	84	80	164
Age categorical			
Units: Subjects			
Children (2-11 years)	84	80	164
Age continuous			
Units: years			
median	3.74	3.80	
standard deviation	± 1.03	± 1.21	-
Gender categorical			
Units: Subjects			
Female	33	35	68
Male	51	45	96
Children included in a social community			
Units: Subjects			
Yes	82	77	159
No	2	3	5
Respiratory system			
Baseline value			
Units: Subjects			
normal	64	61	125
previous abnormal	19	19	38
abnormal in progress	1	0	1
Height			
Units: cm			
median	100.88	101.84	
standard deviation	± 9.49	± 10.05	-
Weight			
Units: kg			
median	16.87	17.68	
standard deviation	± 4.16	± 5.05	-
Recurrent Respiratory Infection in the last year			
Units: number			
median	6.98	6.59	
standard deviation	± 5.58	± 4.47	-
Evaluation of the child's state of well-being (Visual Analog Scale 0-100 mm)			
Units: mm			

median	68.55	68.38	
standard deviation	± 16.34	± 18.34	-

End points

End points reporting groups

Reporting group title	Immucytal/Biomunil group
Reporting group description:	
84 children were randomised in the experimental group.	
Reporting group title	Placebo group
Reporting group description:	
80 children were randomised in the placebo group.	
Subject analysis set title	J022X ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
81 children who have received at least one dose of study drug and have at least one parameter evaluation main after randomization were included in the J022X ITT population.	
Subject analysis set title	Placebo ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
77 children who have received at least one dose of study drug and have at least one parameter evaluation main after randomization were included in the Placebo ITT population	

Primary: Overall duration of infectious episodes during 6 months of treatment

End point title	Overall duration of infectious episodes during 6 months of treatment
End point description:	
Acute infectious episodes affecting the upper respiratory tract, lower respiratory tract or otitis were subjected to clinical evaluation. An episode was defined as new if they occurred at least 72 hours, in the complete absence of symptoms, from the resolution of the previous episode. During each of the 4 visits, the investigator validated the individual diagnoses of acute infectious episodes based on the review of the diaries kept by the parent (or guardian), of the previous telephone contacts, questions asked directly to the parent (or guardian) and the visit made. The missing values have been replaced considering the last value detected (Last Observation carried forward).	
End point type	Primary
End point timeframe:	
The duration of infectious episodes was measured during the study treatment period (6 months).	

End point values	J022X ITT population	Placebo ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	77		
Units: days				
median (standard deviation)	4.4 (± 3.79)	4.44 (± 3.10)		

Statistical analyses

Statistical analysis title	Primary efficacy analysis
Comparison groups	J022X ITT population v Placebo ITT population

Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.91
Method	t-test, 2-sided

Secondary: Duration of infectious episodes during 12 months of observation

End point title	Duration of infectious episodes during 12 months of observation

End point description:

The missing values have been replaced considering the last value detected (Last Observation carried forward).

End point type	Secondary

End point timeframe:

The secondary endpoint was measured during the whole study period (treatment period+ follow-up period).

End point values	J022X ITT population	Placebo ITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	81	77		
Units: days				
median (standard deviation)	4.5 (± 4.02)	4.45 (± 3.18)		

Statistical analyses

Statistical analysis title	Secondary efficacy analysis
Comparison groups	J022X ITT population v Placebo ITT population
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.88
Method	t-test, 2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Any adverse event occuring during the study period was recorded in the CRF.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups	
Reporting group title	J022X Safety population
Reporting group description:	
83 patients who received at least one dose of study treatment were included in the Safety population	
Reporting group title	Placebo Safety population
Reporting group description:	
80 patients who received at least one dose of study treatment were included in the Safety population	

Serious adverse events	J022X Safety population	Placebo Safety population	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 83 (1.20%)	1 / 80 (1.25%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Crush injury			
subjects affected / exposed	0 / 83 (0.00%)	1 / 80 (1.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Acute appendicitis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 80 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	J022X Safety population	Placebo Safety population	
Total subjects affected by non-serious adverse events subjects affected / exposed	47 / 83 (56.63%)	41 / 80 (51.25%)	
Vascular disorders Whitlow subjects affected / exposed occurrences (all)	2 / 83 (2.41%) 2	1 / 80 (1.25%) 1	
Immune system disorders Urticaria subjects affected / exposed occurrences (all)	2 / 83 (2.41%) 2	1 / 80 (1.25%) 1	
Eye disorders Pyrexia subjects affected / exposed occurrences (all)	6 / 83 (7.23%) 6	2 / 80 (2.50%) 2	
Gastrointestinal disorders Gastroenteritis subjects affected / exposed occurrences (all) Enteritis subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	11 / 83 (13.25%) 11 9 / 83 (10.84%) 9 4 / 83 (4.82%) 4	9 / 80 (11.25%) 9 6 / 80 (7.50%) 6 2 / 80 (2.50%) 2	
Respiratory, thoracic and mediastinal disorders Influenza subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all)	8 / 83 (9.64%) 8 5 / 83 (6.02%) 5	7 / 80 (8.75%) 7 2 / 80 (2.50%) 2	
Skin and subcutaneous tissue disorders Impetigo subjects affected / exposed occurrences (all) Scarlet fever	2 / 83 (2.41%) 2	2 / 80 (2.50%) 2	

subjects affected / exposed	2 / 83 (2.41%)	2 / 80 (2.50%)	
occurrences (all)	2	2	
Infections and infestations			
Varicella			
subjects affected / exposed	6 / 83 (7.23%)	6 / 80 (7.50%)	
occurrences (all)	6	6	
Conjunctivitis			
subjects affected / exposed	2 / 83 (2.41%)	3 / 80 (3.75%)	
occurrences (all)	2	3	

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