Clinical trial results:
Clinical efficacy and safety of J022X ST in the prevention of Recurrent Upper-Respiratory Tract Infections (RURTI) in children with a high risk of recurrence

Summary

EudraCT number	2013-001760-31
Trial protocol	IT LT PL RO
Global end of trial date	17 October 2016

Results information

Result version number	v1 (current)
This version publication date	02 May 2017
First version publication date	02 May 2017

Trial information

Trial identification

Sponsor protocol code	J0022XST302

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pierre Fabre Medicament
Sponsor organisation address	45 place Abel Gance, Boulogne, France, 92100
Public contact	Elisabeth Carriere Roussel, IRPF 3 avenue Hubert Curien 31100 Toulouse, +33 5 34 50 63 48,
Scientific contact	Elisabeth Carriere Roussel, IRPF 3 avenue Hubert Curien 31100 Toulouse, +33 5 34 50 63 48,

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	03 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the clinical efficacy of J022X ST in preventing RURTI in young children at risk.

Protection of trial subjects:

This study was performed in accordance with the ethical principles stated in the Declaration of Helsinki (1964 and its subsequent amendments). This study was conducted in agreement with International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines and with applicable national regulations in biomedical research (except in one Romanian centre: see "Recruitment details" caption). The first study protocol version in use , all its amendments, and the patient information sheets, were reviewed by the appropriate independent ethics committees (IECs), including local IECs. This study was placebo-controlled (see rationale in "Evidence for comparator"). In Year 2 of this study, the treatment was proposed only to children having proven recurrent upper respiratory tract infection (RURTI) and for whom it could be beneficial The placebo group received the same medical care as the J00022X group, according to that which would have been provided if they had not participated in this study. If patients showed any early signs of safety concerns or aggravation of symptoms during the study, they were eligible to receive alternative active therapy at any time.

Background therapy:

There was no systematic concomitant administration of any other product than investigational products.

Evidence for comparator:

This study was placebo-controlled as there is still a medical need for alternative treatments As no other product had formally proven its efficacy in prevention of URTIs and could be considered as a reference product, efficacy was assessed vs. placebo. The use of a placebo control was critical to the study to allow
discrimination between patient outcomes caused by J0022XST and outcomes caused by other factors (e.g. the observer or patient expectations, the natural acquisition of immunity, the conditions of study participation).

Actual start date of recruitment	02 September 2013
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	Poland: 197
Country: Number of subjects enrolled	Romania: 365
Country: Number of subjects enrolled	Italy: 114
Country: Number of subjects enrolled	Lithuania: 168
Country: Number of subjects enrolled	Russian Federation: 150
Worldwide total number of subjects	994
EEA total number of subjects	844

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)	994
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:

This phase III study was conducted in two parts: year 1 was an observational phase to select children with RURTI i.e. at least 6 episodes of medically confirmed URTI. year 2: . If eligible, patients were randomised to one of the 2 treatment groups (J022X ST or placebo)

Pre-assignment

Screening details:

53 centres located in 5 countries (France, Hungary, Romania, Latvia, Russian Federation) were initiated, 50 centers had at least one patient included
and 30 recruited patients. . 1003 Children aged 3-4 year, known for RURTI were screened, 994 were included in year 1 (observational phase), 254 were randomised and analysed

Pre-assignment period milestones

Number of subjects started	994
Number of subjects completed	254

Pre-assignment subject non-completion reasons

Reason: Number of subjects	non premature withdrawal not conitnuing: 467
Reason: Number of subjects	premature withdrawal for other reason: 272
Reason: Number of subjects	premature withdrawal for safety: 1

Period 1

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

Blinding implementation details:

Double-blinding was ensured by identical packaging, labelling and administration of the investigational treatments

Arms

Are arms mutually exclusive?	Yes
Arm title	J0022 X ST

Arm description:

experimental

Arm type	Experimental
Investigational medicinal product name	J0022X ST
Investigational medicinal product code	
Other name	Ribomunyl/immucytal/Biomunil
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

- Active substancea: 0.525 mgb, given as ribosomal RNA content.

Ribosomal fractions (10 parts) including:
- Klebsiella pneumoniae (3.5 parts)
- Streptococcus pneumoniae (3 parts)
- Streptococcus pyogenes group A (3 parts)
- Haemophilus influenzae (0.5 parts)

And membrane fraction (15 parts) including:

- Klebsiella pneumoniae.

In the first month of treatment, the patient took one sachet in the morning on an empty stomach for 4 consecutive days per week, for 3 consecutive weeks.

From the second month of treatment, the patient took one sachet in the morning on an empty stomach for 4 consecutive days per month, at monthly intervals, for 5 consecutive months.

Arm title	Placebo
Arm description: -	
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:

In the first month of treatment, the patient took one sachet in the morning on an empty stomach for 4 consecutive days per week, for 3 consecutive weeks. From the second month of treatment, the patient took one sachet in the morning on an empty stomach for 4 consecutive days per month, at monthly intervals, for 5 consecutive months.

Number of subjects in period 1[1]	J0022 X ST	Placebo
Started	122	132
Completed	122	132

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: A total of 740 out of the 994 included patients (73.8%) in year 1 were not randomised in Year 2 due to non premature withdrawal not continuing (467 patients [46.6%]), premature withdrawal for other reason (272 patients [27.1%]) and premature withdrawal for safety reason (one patient [0.1%]). For most patients (609 patients [60.7%]), the categorised reason for non randomisation was because of insufficient URTI épisodes.

Period 2

Period 2 title	year 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	J0022 X ST

Arm description:

experimental

Arm type	Experimental

Investigational medicinal product name	J0022X ST
Investigational medicinal product code	
Other name	Ribomunyl/immucytal/Biomunil
Pharmaceutical forms	Granules
Routes of administration	Oral use

Dosage and administration details:

- Active substancea: 0.525 mgb, given as ribosomal RNA content.

Ribosomal fractions (10 parts) including:
- Klebsiella pneumoniae (3.5 parts)
- Streptococcus pneumoniae (3 parts)
- Streptococcus pyogenes group A (3 parts)
- Haemophilus influenzae (0.5 parts)

And membrane fraction (15 parts) including:
- Klebsiella pneumoniae.

In the first month of treatment, the patient took one sachet in the morning on an empty stomach for 4 consecutive days per week, for 3 consecutive weeks.
From the second month of treatment, the patient took one sachet in the morning on an empty stomach for 4 consecutive days per month, at monthly intervals, for 5 consecutive months.

Arm title	Placebo

Arm description:

Control arm

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:

In the first month of treatment, the patient took one sachet in the morning on an empty stomach for 4 consecutive days per week, for 3 consecutive weeks. From the second month of treatment, the patient took one sachet in the morning on an empty stomach for 4 consecutive days per month, at monthly intervals, for 5 consecutive months.

Number of subjects in period 2	J0022 X ST	Placebo
Started	122	132
Completed	122	132

Baseline characteristics

Reporting groups	
Reporting group title	J0022 X ST
Reporting group description: experimental	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	J0022 X ST	Placebo	Total
Number of subjects	122	132	254
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Age at year 1			
Units: years			
arithmetic mean	3.2	3.3	
standard deviation	± 0.4	± 0.5	-
Gender categorical Units: Subjects			
Female	61	65	126
Male	61	67	128

Subject analysis sets	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

Full Analysis Set (FAS), composed of all patients randomised in Year 2, having received at least one dose of the study treatment. This set was used to perform analyses for efficacy and safety.

Reporting group values	Full analysis set		
Number of subjects	254		
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			

Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age at year 1			
Units: years arithmetic mean standard deviation	 3.2 ± 0.4		
Gender categorical Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	J0022 X ST
Reporting group description: experimental	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	J0022 X ST
Reporting group description: experimental	
Reporting group title	Placebo
Reporting group description: Control arm	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

Full Analysis Set (FAS), composed of all patients randomised in Year 2, having received at least one dose of the study treatment. This set was used to perform analyses for efficacy and safety.

Primary: Difference in the number of URTI between J0022XST and placebo at year 2

End point title	Difference in the number of URTI between J0022XST and placebo at year 2

End point description:

Treatment effect on the number of URTI episodes medically assessed by the Investigator over the 12 months of Year 2 was tested using an analysis of covariance (ANCOVA) model. This model included age at randomisation in Year 2, sex and year of randomisation as covariates, and country as stratum factor. The primary analysis was performed on the FAS and repeated on the PP Set as a supportive analysis.

End point type	Primary

End point timeframe:

The main statistical objective was to show a difference in the number of URTIs in Year 2 between J022X ST and placebo on the FAS.

End point values	J0022 X ST	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	132		
Units: ajusted mean difference	122	132		

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

Treatment effect on the number of URTI episodes medically assessed by the Investigator over the 12 months of Year 2 was tested using an analysis of covariance (ANCOVA) model. This model included age at randomisation in Year 2, sex and year of randomisation as covariates, and country as stratum factor. The primary analysis was performed on the FAS and repeated on the PP Set as a supportive analysis.

Comparison groups	J0022 X ST v Placebo

Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.21
Method	ANCOVA
Parameter estimate	Median difference (net)
Point estimate	-0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	-0.18
Variability estimate	Standard error of the mean
Dispersion value	0.25

Notes:

[1] - The main statistical objective was to show a difference in the number of URTIs in Year 2 between J022X ST and placebo on the FAS with the following null hypothesis H0a: there was no difference between treatments in the number of URTIs in Year 2 vs. H1a: there was a difference between treatments.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation to End of Study Visit (expected to be V10/D50 or V9/D43 the End of Treatment Visit if the patient did not enter the follow-up)

Adverse event reporting additional description:

AEs and AEs other than URTIs, reported in Year 2 : i.e. defined as any AEs started after the Randomisation visit of Year 2 or ongoing at the Randomisation visit of Year 2

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	J0022 X ST

Reporting group description:

experimental

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	J0022 X ST	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 122 (0.00%)	2 / 132 (1.52%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
appendicitis			
subjects affected / exposed	0 / 122 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 122 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acetonaemia	Additional description: the same patient presented constipation, acetonaemia and gastritis leading to hospitalisation beacause of abdominal pain		
subjects affected / exposed	0 / 122 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			

subjects affected / exposed	0 / 122 (0.00%)	1 / 132 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2.5 %

Non-serious adverse events	J0022 X ST	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	93 / 122 (76.23%)	97 / 132 (73.48%)	
Gastrointestinal disorders			
Enterocolitis			
subjects affected / exposed	7 / 122 (5.74%)	6 / 132 (4.55%)	
occurrences (all)	7	7	
Diarrhoea			
subjects affected / exposed	1 / 122 (0.82%)	3 / 132 (2.27%)	
occurrences (all)	1	3	
Infections and infestations			
Tonsilitis			
subjects affected / exposed	45 / 122 (36.89%)	45 / 132 (34.09%)	
occurrences (all)	77	63	
Nasopharyngitis			
subjects affected / exposed	35 / 122 (28.69%)	36 / 132 (27.27%)	
occurrences (all)	52	64	
Laryngitis			
subjects affected / exposed	35 / 122 (28.69%)	36 / 132 (27.27%)	
occurrences (all)	52	64	
Otitis media acute			
subjects affected / exposed	18 / 122 (14.75%)	17 / 132 (12.88%)	
occurrences (all)	23	23	
Pharyngitis			
subjects affected / exposed	14 / 122 (11.48%)	13 / 132 (9.85%)	
occurrences (all)	19	17	
Varicela			
subjects affected / exposed	10 / 122 (8.20%)	5 / 132 (3.79%)	
occurrences (all)	10	5	
Upper respiratory tract infection			

subjects affected / exposed	8 / 122 (6.56%)	13 / 132 (9.85%)	
occurrences (all)	25	27	
Sinusitis			
subjects affected / exposed	6 / 122 (4.92%)	13 / 132 (9.85%)	
occurrences (all)	8	16	
Bronchitis			
subjects affected / exposed	5 / 122 (4.10%)	8 / 132 (6.06%)	
occurrences (all)	8	9	
Rhinitis			
subjects affected / exposed	5 / 122 (4.10%)	7 / 132 (5.30%)	
occurrences (all)	6	8	
Otitis media			
subjects affected / exposed	4 / 122 (3.28%)	1 / 132 (0.76%)	
occurrences (all)	5	1	
Conjuncivitis			
subjects affected / exposed	3 / 122 (2.46%)	4 / 132 (3.03%)	
occurrences (all)	4	4	
Pneumonia			
subjects affected / exposed	3 / 122 (2.46%)	2 / 132 (1.52%)	
occurrences (all)	3	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 March 2014	Addition of the CROs involved in the study Update of the planned study period according to the approval from AIFA Precision on inclusion and non-inclusion criteria (e.g. other diseases and relating to treatments) Precision on premature withdrawal visits of Year 1 and Year 2 Correction of flow-chart Addition of the Interactive Web Response System (IWRS) procedure Addition of information due to the modification of the safety document reference (Italian Summary of Product CharacteristicsSafety section of the Investigator's Brochure as requested by Russian Authorities Addition of requests made by the Russian Ministry of Health Change of Clinical Study Manager and modification of the Corporate Safety Officer's contact details Removal of information on the Head of Therapeutic Area
17 July 2014	Addition of paracetamol and NSAIDs for URTI as authorised treatments Clarification that ibuprofen had to be prescribed at more than 30 mg/kg/day in the definition of a severe URTI Clarification that anti-histamines could be prescribed during the study Addition of information on test product quantity Removal of the IWRS and update of the treatment number allocation procedure Replacement of the Medical Study Manager by the Clinical Program Director

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported