



Clinical trial results:

Efficacy and tolerability clinical trial of an immunostimulant made from inactivated bacteria (BUCCALIN) in the prophylaxis of infection of the airways (rhinotracheobronchitis, colds). Double-blind multicenter, randomized study vs. placebo.

Summary

EudraCT number	2011-005187-25
Trial protocol	IT
Global end of trial date	05 September 2013

Results information

Result version number	v1 (current)
This version publication date	18 July 2020
First version publication date	18 July 2020

Trial information

Trial identification

Sponsor protocol code	BUC-SI-11-001
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Laboratorio Farmaceutico S.I.T. Srl
Sponsor organisation address	Via Cavour 70, Mede (PV), Italy, 27035
Public contact	Ricerca Clinica, Medi Service SRL, 0039 039 6057074, medi@mediservice.it
Scientific contact	Ricerca Clinica, Medi Service SRL, 0039 039 6057074, medi@mediservice.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	16 February 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 September 2013
Global end of trial reached?	Yes
Global end of trial date	05 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Comparison, vs placebo, during 6 months of the infective episodes of the respiratory tract (number of days of illness) from the day of the first dose. Number of illness days recorded by the patient on a special diary.

Protection of trial subjects:

During the study period, to minimise the patients pain/distress, it was permitted to take the following concomitant medications:
antibiotics, anti-inflammatory, bronchodilators, decongestant, mucolytics.

The subject's wellbeing was evaluated at month 4 and month 6.

Background therapy:

During the two weeks preceding the randomization the following drugs were not allowed:
Immunestimulants, gamma-globulines, etc. of the ATC group J06 and J07AX; Anti-neoplastic drugs of the ATC group L01; Cytokines, interleukins, interferon, immune-suppressants of the ATC group L03 and L04.

After the randomization and during the study (including the follow-up period) the following drugs were not permitted:

Immune-stimulants of the ATC group J07AX; Anti-neoplastic drugs of the ATC group L01; Cytokines, interleukins, interferon, immune-suppressants of the ATC group L03 and L04; Systemic steroids (if used for more than 2 weeks); Any drug product or dietary supplement containing zinc (if used for more than one week); Any other product with immune-stimulant features.

Evidence for comparator:

To minimise the patients pain/distress, it was permitted to take the following concomitant medications:
antibiotics, anti-inflammatory, bronchodilators, decongestant, mucolytics.

Actual start date of recruitment	01 February 2012
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: 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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	176
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 187 subjects were enrolled in 10 Italian Clinical Centres in the period September 2012 - September 2013.

The Full Analysis Set (FAS) population consisted of 178 subjects (88 assigned to placebo and 90 to Buccalin).

Pre-assignment

Screening details:

Run-in and/or screening periods were not planned in the study design. Randomization visit (Visit 1) was considered as baseline visit.

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, Monitor

Blinding implementation details:

This study had a double blind design. A computer generated randomisation list in blocks of 4, to balance the random allocation to each treatment, was managed by CRO. A duly closed and sealed copy of randomisation list was kept by the Sponsor.

Each Investigator received a set of sealed envelopes, one for each subject assigned to his/her centre.

Each envelope contained the identity of subject's treatment, formed by a three-digit number.

Arms

Are arms mutually exclusive?	Yes
Arm title	Buccalin

Arm description:

Buccalin is constituted by mixture of:

Streptococcus pneumonia I, II, III: 1×10^9 inactivated bacterial bodies

Streptococcus haemolyticus (agalactiae): 1×10^9 inactivated bacterial bodies

Staphylococcus aureus: 1×10^9 inactivated bacterial bodies

Hemophilus influenza: 1.5×10^9 inactivated bacterial bodies

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

Dosage and administration details:

Administration: first three days of each of the four treatment cycles according to the following scheme: one tablet on day 1, two tablets on day 2, four tablets on day 3.

Arm title	placebo
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Arm description:

The placebo consisted of gastroresistant tablets containing only excipients (lactose, micro.-crystalline cellulose).

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

Dosage and administration details:

Administration: first three days of each of the four treatment cycles according to the following scheme: one tablet on day 1, two tablets on day 2, four tablets on day 3.

Number of subjects in period 1	Buccalin	placebo
Started	90	88
Completed	84	86
Not completed	6	2
Consent withdrawn by subject	1	1
Adverse event, non-fatal	4	-
Lost to follow-up	-	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups

Reporting group title	Buccalin
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Reporting group description:

Buccalin is constituted by mixture of:

Streptococcus pneumonia I, II, III: 1×10^9 inactivated bacterial bodies

Streptococcus haemolyticus (agalactiae): 1×10^9 inactivated bacterial bodies

Staphylococcus aureus: 1×10^9 inactivated bacterial bodies

Hemophilus influenza: 1.5×10^9 inactivated bacterial bodies

Reporting group title	placebo
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Reporting group description:

The placebo consisted of gastroresistant tablets containing only excipients (lactose, micro.-crystalline cellulose).

Reporting group values	Buccalin	placebo	Total
Number of subjects	90	88	178
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	90	86	176
From 65-84 years	0	2	2
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	48.4	48.5	
standard deviation	± 11.6	± 12.9	-
Gender categorical Units: Subjects			
Female	49	50	99
Male	41	38	79
Previous (1 year) infectious episodes of airways Units: Subjects			
2 infectious episodes	11	10	21
3 infectious episodes	22	28	50
4 infectious episodes	20	24	44
5 infectious episodes	18	12	30
6 infectious episodes	19	14	33
Smoking history Units: Subjects			
Current smoker	12	15	27
Passive smoker	16	10	26

No smoker	62	63	125
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End points

End points reporting groups

Reporting group title	Buccalin
Reporting group description: Buccalin is constituted by mixture of: Streptococcus pneumonia I, II, III: 1×10^9 inactivated bacterial bodies Streptococcus haemolyticus (agalactiae): 1×10^9 inactivated bacterial bodies Staphylococcus aureus: 1×10^9 inactivated bacterial bodies Hemophilus influenza: 1.5×10^9 inactivated bacterial bodies	
Reporting group title	placebo
Reporting group description: The placebo consisted of gastroresistant tablets containing only excipients (lactose, micro.-crystalline cellulose).	

Primary: Number of days with infectious disease

End point title	Number of days with infectious disease
End point description:	
End point type	Primary
End point timeframe: Study period = 6 months	

End point values	Buccalin	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90 ^[1]	88 ^[2]		
Units: number				
arithmetic mean (standard deviation)	6.6 ($\pm$ 8.0)	7.5 ($\pm$ 10.6)		

Notes:

[1] - Full Analysis Set

[2] - Full Analysis Set

Statistical analyses

Statistical analysis title	Primary efficacy analysis
Statistical analysis description: The primary study objective was to the comparison between the test drug (Buccalin) and placebo of the number of days with respiratory infections in the follow-up period of 6 months, starting from the beginning of treatment, as recorded in the subject's diary.	
Comparison groups	Buccalin v placebo

Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032 ^[3]
Method	ANCOVA
Parameter estimate	Estimated Marginal Means difference
Point estimate	-1.724
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.293
upper limit	-0.154
Variability estimate	Standard error of the mean
Dispersion value	0.795

Notes:

[3] - Analysis of Covariance (ANCOVA)

Dependent variable: number of days with respiratory infections in the follow-up period of 6 months

Factor: treatment group

Covariates: number of previous infections and total number of infectious episodes

Secondary: Total number of infectious episodes

End point title	Total number of infectious episodes
End point description:	
Number of respiratory infectious episodes at 6 months	
End point type	Secondary
End point timeframe:	
Study period = 6 months	

End point values	Buccalin	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90 ^[4]	88 ^[5]		
Units: number				
arithmetic mean (standard deviation)	1.1 (± 1.2)	0.9 (± 1.2)		

Notes:

[4] - Full Analysis Set

[5] - Full Analysis Set

Statistical analyses

Statistical analysis title	Secondary efficacy analysis
Statistical analysis description:	
Number of respiratory infectious episodes at 6 months.	
Comparison groups	Buccalin v placebo
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.671 ^[6]
Method	ANCOVA
Parameter estimate	Estimated Marginal Means difference
Point estimate	0.077

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.279
upper limit	0.433
Variability estimate	Standard error of the mean
Dispersion value	0.181

Notes:

[6] - Analysis of Covariance (ANCOVA):

Dependent variable: total number of infectious episodes

Factor: treatment group

Covariate: number of previous infectious episodes

Secondary: Severity of infectious episodes (month 0-4)

End point title	Severity of infectious episodes (month 0-4)
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End point description:

End point type	Secondary
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End point timeframe:

Month 0-4

End point values	Buccalin	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	88		
Units: number				
mild	47	38		
moderate	43	38		
severe	1	1		

Statistical analyses

Statistical analysis title	Secondary efficacy analysis
Comparison groups	placebo v Buccalin
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.953
Method	Chi-squared

Secondary: Severity of infectious episodes (month 4-6)

End point title	Severity of infectious episodes (month 4-6)
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End point description:

End point type	Secondary
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End point timeframe:

Month 4-6

End point values	Buccalin	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90 ^[7]	88 ^[8]		
Units: number				
mild	3	6		
moderate	3	3		
severe	1	1		

Notes:

[7] - Full Analysis Set

[8] - Full Analysis Set

Statistical analyses

Statistical analysis title	Secondary efficacy analysis
Comparison groups	Buccalin v placebo
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.784
Method	Chi-squared

Secondary: Global efficacy, evaluated by the Investigator

End point title	Global efficacy, evaluated by the Investigator
End point description:	
End point type	Secondary
End point timeframe:	
Study period = 6 months	

End point values	Buccalin	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90 ^[9]	88 ^[10]		
Units: number				
Worsened	0	1		
Unchanged	10	7		
Improved	47	53		
Markedly improved	27	25		

Notes:

[9] - Full Analysis Set

For 6 subjects the value is missing

[10] - Full Analysis Set

For 2 subjects the value is missing

Statistical analyses

Statistical analysis title	Secondary efficacy analysis
Comparison groups	Buccalin v placebo
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.584
Method	Chi-squared

Secondary: Global safety, evaluated by the Patient

End point title	Global safety, evaluated by the Patient
End point description:	
End point type	Secondary
End point timeframe:	
Study period = 6 months	

End point values	Buccalin	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90 ^[11]	88 ^[12]		
Units: number				
Excellent	44	47		
Good	39	37		
Fair	1	2		

Notes:

[11] - Full Analysis Set

For 6 subjects the value is missing

[12] - Full Analysis Set

For 2 subjects the value is missing

Statistical analyses

Statistical analysis title	Secondary efficacy analysis
Comparison groups	Buccalin v placebo

Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.794
Method	Chi-squared

Secondary: General well-being, evaluated by the Patient

End point title	General well-being, evaluated by the Patient
End point description:	
End point type	Secondary
End point timeframe:	
Study period = 6 months	

End point values	Buccalin	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90 ^[13]	88 ^[14]		
Units: number				
arithmetic mean (standard deviation)	7.7 ($\pm$ 1.39)	7.8 ($\pm$ 1.33)		

Notes:

[13] - Full Analysis Set

[14] - Full Analysis Set

Statistical analyses

Statistical analysis title	Secondary efficacy analysis
Comparison groups	Buccalin v placebo
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.724 ^[15]
Method	t-test, 2-sided

Notes:

[15] - Independent samples t-test p-value

Secondary: Number of days lost at work or school

End point title	Number of days lost at work or school
End point description:	
End point type	Secondary
End point timeframe:	
Study period = 6 months	

End point values	Buccalin	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90 ^[16]	88 ^[17]		
Units: number				
arithmetic mean (standard deviation)	1.3 (± 3.45)	1.0 (± 2.5)		

Notes:

[16] - Full Analysis Set

[17] - Full Analysis Set

Statistical analyses

Statistical analysis title	Secondary efficacy analysis
Comparison groups	Buccalin v placebo
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.461 ^[18]
Method	t-test, 2-sided

Notes:

[18] - Independent samples t-test p-value

Secondary: Disease free period

End point title	Disease free period
End point description:	Disease free period, evaluated as the time of occurrence of the first infectious episode after the end of the treatment cycles.
End point type	Secondary
End point timeframe:	Study period = 6 months

End point values	Buccalin	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90 ^[19]	88 ^[20]		
Units: number				
number (confidence interval 95%)	138.0 (126.5 to 149.5)	128.1 (113.7 to 142.5)		

Notes:

[19] - Full Analysis Set

[20] - Full Analysis Set

Statistical analyses

Statistical analysis title	Secondary efficacy analysis
Comparison groups	Buccalin v placebo

Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.302
Method	Logrank

Secondary: Use of anti-inflammatory

End point title	Use of anti-inflammatory
End point description:	
End point type	Secondary
End point timeframe:	
Study period = 6 months	

End point values	Buccalin	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90 ^[21]	88 ^[22]		
Units: number				
No	56	53		
Yes	34	35		

Notes:

[21] - Full Analysis Set

[22] - Full Analysis Set

Statistical analyses

Statistical analysis title	Secondary efficacy analysis
Comparison groups	Buccalin v placebo
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.785
Method	Chi-squared
Parameter estimate	Cox proportional hazard

Secondary: Use of bronchodilators

End point title	Use of bronchodilators
End point description:	
End point type	Secondary
End point timeframe:	
Study period = 6 months	

End point values	Buccalin	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90 ^[23]	88 ^[24]		
Units: number				
No	79	76		
Yes	11	12		

Notes:

[23] - Full Analysis Set

[24] - Full Analysis Set

Statistical analyses

Statistical analysis title	Secondary efficacy analysis
Comparison groups	Buccalin v placebo
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.779
Method	Chi-squared

Secondary: Use of antibiotics

End point title	Use of antibiotics
End point description:	
End point type	Secondary
End point timeframe:	
Study period = 6 months	

End point values	Buccalin	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90 ^[25]	88 ^[26]		
Units: number				
No	55	57		
Yes	35	31		

Notes:

[25] - Full Analysis Set

[26] - Full Analysis Set

Statistical analyses

Statistical analysis title	Secondary efficacy analysis
Comparison groups	Buccalin v placebo

Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.613
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Study period = 6 months

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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Reporting groups

Reporting group title	Buccalin
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Reporting group description: -

Reporting group title	placebo
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Reporting group description: -

Serious adverse events	Buccalin	placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 91 (0.00%)	1 / 90 (1.11%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia	Additional description: pneumonia		
subjects affected / exposed	0 / 91 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Buccalin	placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 91 (18.68%)	10 / 90 (11.11%)	
General disorders and administration site conditions			
Pyrexia	Additional description: Fever		
subjects affected / exposed	1 / 91 (1.10%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Fatigue	Additional description: Fatigue		

subjects affected / exposed	0 / 91 (0.00%)	3 / 90 (3.33%)	
occurrences (all)	0	6	
Chest pain			
subjects affected / exposed	0 / 91 (0.00%)	1 / 90 (1.11%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain upper	Additional description: Gastric pain		
subjects affected / exposed	5 / 91 (5.49%)	2 / 90 (2.22%)	
occurrences (all)	5	2	
Diarrhoea			
subjects affected / exposed	4 / 91 (4.40%)	0 / 90 (0.00%)	
occurrences (all)	4	0	
Toothache	Additional description: Tooth pain		
subjects affected / exposed	1 / 91 (1.10%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Influenza	Additional description: Flu syndrome		
subjects affected / exposed	2 / 91 (2.20%)	0 / 90 (0.00%)	
occurrences (all)	2	0	
Bronchitis	Additional description: Acute bronchitis		
subjects affected / exposed	2 / 91 (2.20%)	2 / 90 (2.22%)	
occurrences (all)	2	2	
Skin and subcutaneous tissue disorders			
Herpes zoster			
subjects affected / exposed	1 / 91 (1.10%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Pruritus allergic	Additional description: Skin allergy		
subjects affected / exposed	1 / 91 (1.10%)	1 / 90 (1.11%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: Back pain		
subjects affected / exposed	1 / 91 (1.10%)	0 / 90 (0.00%)	
occurrences (all)	1	0	
Bone pain			
subjects affected / exposed	2 / 91 (2.20%)	1 / 90 (1.11%)	
occurrences (all)	2	1	

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