Clinical trial results:
Combined treatment with pidotimod and bifidobacteria in pre-scholastic age children with recurrent respiratory infections: evaluation of clinical efficacy and parents' quality of life

Summary

EudraCT number	2015-002733-22
Trial protocol	IT
Global end of trial date	27 July 2017

Results information

Result version number	v1 (current)
This version publication date	28 June 2018
First version publication date	28 June 2018

Trial information

Trial identification

Sponsor protocol code	MB0515/1021/03

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	VALEAS SPA
Sponsor organisation address	Via Vallisneri 10, MILANO, Italy, 20133
Public contact	Clinical Department, VALEAS SPA, 0039 0223690215, dir.medica@valeas.it
Scientific contact	Clinical Department, VALEAS SPA, 0039 0223690215, dir.medica@valeas.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	02 October 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate in pre-scholastic age children with recurrent respiratory infections the effects of the treatment with pidotimod and/or bifidobacteria on the prevention of respiratory infections.

Protection of trial subjects:

At each visit, the investigator will evaluate the data reported in the diary to determine if and how many respiratory infections or what and how many adverse events will occur.

Background therapy:

All drugs that subjects intake before enrollment are admitted, except immonu-modulating drugs, corticosteroids (except inhaled corticosteroids)

Evidence for comparator: -

Actual start date of recruitment	16 October 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	2 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 98
Worldwide total number of subjects	98
EEA total number of subjects	98

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)	98
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:

All patients (n. 98) were recruited in Italy.

Pre-assignment

Screening details:

Children, aged 3-6 years, who go to the school and have recurrent respiratory infections in the last previous year were included. A total of 98 patients were randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment A

Arm description:

Pidotimod + Bifidobacteri

Arm type	Experimental
Investigational medicinal product name	Pidotimod
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution in single-dose container
Routes of administration	Oral use

Dosage and administration details:

1 single-dose container 400 mg, oral administration between meals, for 10 days at month for 4 months

Investigational medicinal product name	Bifidobacterium longum BB536, Bifidobacterium infantis M-63, Bifidobacterium breve M-16V
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules for oral suspension in sachet
Routes of administration	Oral use

Dosage and administration details:

1 sachet/die 5 billion Units in 3 g, oral administration between meals, 10 days at month for 4 months

Arm title	Treatment B

Arm description:

Pidotimod + Placebo Pro

Arm type	Experimental
Investigational medicinal product name	Pidotimod
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution in single-dose container
Routes of administration	Oral use

Dosage and administration details:

1 single-dose container 400 mg, oral administration between meals, for 10 days at month for 4 months

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

Dosage and administration details:

1 sachet/ die, oral administration between meals, for 10 days at month for 4 months

Arm title	Treatment C

Arm description:

Placebo Imm + Bifidobacteri

Arm type	Experimental
Investigational medicinal product name	Bifidobacterium longum BB536, Bifidobacterium infantis M-63, Bifidobacterium breve M-16V
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules for oral suspension in sachet
Routes of administration	Oral use

Dosage and administration details:

1 sachet/die 5 billion Units in 3 g, oral administration between meals, 10 days at month for 4 months

Investigational medicinal product name	Placebo Immunomodulant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution in single-dose container
Routes of administration	Oral use

Dosage and administration details:

1 single-dose container, oral administration between meals, 10 days at month for 4 months

Arm title	Treatment D

Arm description:

Placebo Pro + Placebo Imm

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

Dosage and administration details:

1 sachet/ die, oral administration between meals, for 10 days at month for 4 months

Investigational medicinal product name	Placebo Immunomodulant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution in single-dose container
Routes of administration	Oral use

Dosage and administration details:

1 single-dose container, oral administration between meals, for 10 days at month for 4 months

Number of subjects in period 1	Treatment A	Treatment B	Treatment C
Started	25	25	23
Completed	13	13	13
Not completed	12	12	10
Lost to follow-up	12	12	10

Number of subjects in period 1	Treatment D
Started	25
Completed	16
Not completed	9
Lost to follow-up	9

Baseline characteristics

Reporting groups	
Reporting group title	Treatment A
Reporting group description: Pidotimod + Bifidobacteri	
Reporting group title	Treatment B
Reporting group description: Pidotimod + Placebo Pro	
Reporting group title	Treatment C
Reporting group description: Placebo Imm + Bifidobacteri	
Reporting group title	Treatment D
Reporting group description: Placebo Pro + Placebo Imm	

Reporting group values	Treatment A	Treatment B	Treatment C
Number of subjects	25	25	23
Age categorical Units: Subjects			
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)	25	25	23
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	3.7	3.8	3.7
full range (min-max)	3 to 6	3 to 6	3 to 6
Gender categorical Units: Subjects			
Female	11	9	10
Male	14	16	13
Upper Tract Respiratory Infection			
Respiratory infections in the upper tract, which occurred during the previous year.			
Units: number			
arithmetic mean	7.16	6.92	7.78
full range (min-max)	1 to 13	1 to 13	1 to 18
Lower Tract Respiratory Infection			
Respiratory infections in the lower tract, which occurred during the previous year.			
Units: number			
arithmetic mean	0.96	1.24	0.74
full range (min-max)	0 to 9	0 to 6	0 to 6

Reporting group values	Treatment D	Total	
Number of subjects	25	98	
Age categorical Units: Subjects			
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)	25	98	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	3.7		
full range (min-max)	3 to 6	-	
Gender categorical Units: Subjects			
Female	12	42	
Male	13	56	
Upper Tract Respiratory Infection			
Respiratory infections in the upper tract, which occurred during the previous year.			
Units: number			
arithmetic mean	7.48		
full range (min-max)	5 to 12	-	
Lower Tract Respiratory Infection			
Respiratory infections in the lower tract, which occurred during the previous year.			
Units: number			
arithmetic mean	1.12		
full range (min-max)	0 to 5	-	

Subject analysis sets

Subject analysis set title	Intention-to-treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients who intake at least one dose of medication are included in the Intention-to-treat group

Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol

Subject analysis set description:

All patients who have the last visit after 6 months from randomization (4 months of treatment + 2 months of follow-up).

Reporting group values	Intention-to-treat	Per Protocol	
Number of subjects	98	55	
Age categorical Units: Subjects			
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)	98	55	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	3.8	3.8	
full range (min-max)	3 to 6	3 to 6	
Gender categorical			
Units: Subjects			
Female	42	21	
Male	56	34	
Upper Tract Respiratory Infection			
Respiratory infections in the upper tract, which occurred during the previous year.			
Units: number			
arithmetic mean	7.33	6.88	
full range (min-max)	1 to 18	1 to 13	
Lower Tract Respiratory Infection			
Respiratory infections in the lower tract, which occurred during the previous year.			
Units: number			
arithmetic mean	1.02	1.00	
full range (min-max)	0 to 9	0 to 9	

End points

End points reporting groups	
Reporting group title	Treatment A
Reporting group description: Pidotimod + Bifidobacteri	
Reporting group title	Treatment B
Reporting group description: Pidotimod + Placebo Pro	
Reporting group title	Treatment C
Reporting group description: Placebo Imm + Bifidobacteri	
Reporting group title	Treatment D
Reporting group description: Placebo Pro + Placebo Imm	
Subject analysis set title	Intention-to-treat
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients who intake at least one dose of medication are included in the Intention-to-treat group	
Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description: All patients who have the last visit after 6 months from randomization (4 months of treatment + 2 months of follow-up).	

Primary: Number of Upper Tract Respiratory Infection	
End point title	Number of Upper Tract Respiratory Infection
End point description: This analysis has been performed in the Per Protocol population	
End point type	Primary
End point timeframe: From randomization to the end of follow-up (6 months)	

End point values	Treatment A	Treatment B	Treatment C	Treatment D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	13	13	16
Units: number				
arithmetic mean (confidence interval 95%)	3.0 (1.9 to 4.1)	4.1 (2.6 to 5.6)	4.9 (3.8 to 6.0)	3.6 (2.9 to 4.3)

Statistical analyses

Statistical analysis title	Treatment A vs Treatment D
Comparison groups	Treatment A v Treatment D

Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	> 0.05
Method	ANOVA

Notes:

[1] - No statistical difference has been detected after ANOVA test

Statistical analysis title	Treatment A vs Treatment B
Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	> 0.05
Method	ANOVA

Notes:

[2] - No statistical difference has been detected after ANOVA test

Statistical analysis title	Treatment A vs Treatment C
Comparison groups	Treatment A v Treatment C
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	> 0.05
Method	ANOVA

Notes:

[3] - No statistical difference has been detected after ANOVA test

Secondary: Duration of Upper Tract Respiratory Infection	
End point title	Duration of Upper Tract Respiratory Infection
End point description:	
This analysis has been performed on Per Protocol Population	
End point type	Secondary
End point timeframe:	
From randomization to the end of follow-up (6 months)	

End point values	Treatment A	Treatment B	Treatment C	Treatment D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	13	13	16
Units: day				
arithmetic mean (confidence interval 95%)	21.2 (9.3 to 33.2)	24.6 (10.8 to 38.4)	36.6 (25.3 to 47.9)	32.2 (18.7 to 45.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of days with Upper Tract Respiratory Infection	
End point title	Percent of days with Upper Tract Respiratory Infection
End point description:	
This analysis has been performed on Per Protocol Population	
End point type	Secondary
End point timeframe:	
From randomization to the end of follow-up (6 months)	

End point values	Treatment A	Treatment B	Treatment C	Treatment D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	13	13	16
Units: percent				
arithmetic mean (confidence interval 95%)	11.9 (5.5 to 18.2)	14.3 (6.1 to 22.4)	20.2 (14.2 to 26.1)	17.4 (10.7 to 24.1)

Statistical analyses

Statistical analysis title	Treatment A vs Treatment D
Comparison groups	Treatment A v Treatment D
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	> 0.05
Method	ANOVA

Notes:

[4] - No significant difference has been detected in the ANOVA test

Statistical analysis title	Treatment A vs Treatment B
Comparison groups	Treatment A v Treatment B
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	> 0.05
Method	ANOVA

Notes:

[5] - No significant difference has been detected in the ANOVA test

Statistical analysis title	Treatment A vs Treatment C
Comparison groups	Treatment A v Treatment C

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	> 0.05
Method	ANOVA

Notes:

[6] - No significant difference has been detected in the ANOVA test

Secondary: Duration of each episode of Upper Tract Respiratory Infection

End point title	Duration of each episode of Upper Tract Respiratory Infection

End point description:

This analysis has been performed on Per Protocol Population

End point type	Secondary

End point timeframe:

From randomization to the end of follow-up (6 months)

End point values	Treatment A	Treatment B	Treatment C	Treatment D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	13	13	16
Units: day				
arithmetic mean (confidence interval 95%)	7.39 (2.8 to 12.0)	4.74 (2.7 to 6.7)	8.01 (5.4 to 10.6)	8.04 (4.9 to 11.1)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From randomization to the end of follow-up (6 months)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Intention-to-treat

Reporting group description:

All patients who received at least a dose of study drug were included in the analysis.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: None non-serious adverse event has been reported during the study

Serious adverse events	Intention-to-treat		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 98 (1.02%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 98 (1.02%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	Intention-to-treat		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 98 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 June 2016	Substantial amendment to protocol was required to assess the metabolomic profile of urine before and after treatment and to prolong the enrolment period in order to reach the adequate population size. The sections of protocol amended were: rational, secondary endpoints, secondary variables, study procedure. The informed consent was consistently modified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported