Clinical trial results:
Otitis Media and Nasopharyngeal Microbiome in Children.

The change of nasopharyngeal microbiome and its role as a risk factor of otitis media. Streptococcus salivarius K12 and the change of nasopharyngeal microbiome.

Summary

EudraCT number	2017-000820-83
Trial protocol	FI
Global end of trial date	25 November 2017

Results information

Result version number	v1 (current)
This version publication date	21 August 2024
First version publication date	21 August 2024
Summary attachment (see zip file)	Article file (inf-40-0394.pdf)

Trial information

Trial identification

Sponsor protocol code	NNL-2017

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University of Oulu
Sponsor organisation address	PO BOX 8000, Oulu, Finland, 90014
Public contact	PEDEGO/Lasten ja nuorten klinikka, Oulu University Hospital, +358 83152011,
Scientific contact	PEDEGO/Lasten ja nuorten klinikka, Oulu University Hospital/ University of Oulu, +358 83152011,

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	31 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 November 2017
Global end of trial reached?	Yes
Global end of trial date	25 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

We investigate the role of microbiota as a risk factor of acute otitis media in children. We conclude the acceptability and microbial efficiency (change in the microbiome of nasopharyngeal/oral cavity) of two Streptococcus salivarius K12 BLIS products in children.

Protection of trial subjects:

Normal protection under the laws of Finland.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 October 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
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	Finland: 121
Worldwide total number of subjects	121
EEA total number of subjects	121

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)	25
Children (2-11 years)	96
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:

Randomly allocated to a treatment (S. salivarius K12) or control group 2:1. Children ≤3 years old were randomly allocated to receive either S. salivarius K12 soluble powder or no treatment and older children were randomly allocated to receive S. salivarius K12 chewable tablets or no treatment.

Pre-assignment

Screening details:

We sent information letters about the clinical trial to all the parents of children 1–6 years of age who attended 15 daycare centers in the city of Oulu, Finland. We attended parents' meetings in daycare centers. We excluded children with present chronic secretory otitis media or other middle ear effusionat study entry.

Period 1

Period 1 title	Recruitment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Data analyst[1]

Blinding implementation details:

The study design of this research was a randomized controlled clinical trial that was open to the families but blinded for the microbiologic analyses.

Arms

Are arms mutually exclusive?	Yes
Arm title	Streptococcus salivarius K12

Arm description:

S. salivarius K12 oral soluble powder or tablet for 30 days

Arm type	Experimental
Investigational medicinal product name	Streptococcus salivarius K12
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder in sachet
Routes of administration	Oral use

Dosage and administration details:

1 sachet per day for 30 days

Investigational medicinal product name	Streptococcus salivarius K12
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable/dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet per day in the evening after teeth brushing for 30 days.

Arm title	No treatment

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This trial was blinded for the microbiological analyses but open for the families.

Number of subjects in period 1	Streptococcus salivarius K12	No treatment
Started	81	40
Completed	81	40

Period 2	
Period 2 title	Study period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Data analyst[2]
Arms	
Are arms mutually exclusive?	Yes
Arm title	Streptococcus salivarius K12
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Streptococcus salivarius K12
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder in sachet
Routes of administration	Oral use
Dosage and administration details: 1 sachet per day for 30 days	
Arm title	No treatment
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Notes:

[2] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This trial was blinded for the microbiological analyses but open for the families.

Number of subjects in period 2	Streptococcus salivarius K12	No treatment
Started	81	40
Completed	81	40

Period 3	
Period 3 title	Follow-up period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Data analyst[3]

Arms	
Are arms mutually exclusive?	Yes
Arm title	Streptococcus salivarius K12

Arm description:

S. salivarius treatment, ended

Arm type	Experimental
Investigational medicinal product name	Streptococcus salivarius K12
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral powder in sachet
Routes of administration	Oral use

Dosage and administration details:

1 sachet per day for 30 days

Arm title	No treatment

Arm description:

No treatment, follow-up

Arm type	No intervention

No investigational medicinal product assigned in this arm

Notes:

[3] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This trial was blinded for the microbiological analyses but open for the families.

Number of subjects in period 3	Streptococcus salivarius K12	No treatment
Started	81	40
Completed	81	40

Baseline characteristics

Reporting groups	
Reporting group title	Streptococcus salivarius K12
Reporting group description:	
S. salivarius K12 oral soluble powder or tablet for 30 days	
Reporting group title	No treatment
Reporting group description: -	

Reporting group values	Streptococcus salivarius K12	No treatment	Total
Number of subjects	81	40	121
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			
Units: years			
arithmetic mean	4.2	3.5	
standard deviation	± 1.5	± 1.5	-
Gender categorical			
Units: Subjects			
Female	40	18	58
Male	41	22	63
Parental smoking (yes)			
Units: Subjects			
Parental smoking (yes)	13	4	17
parental smoking (no)	68	36	104
Pacifier			
Pacifier use ever			
Units: Subjects			
Pacifier use	57	25	82
No pacifier use or no data	24	15	39
Breast-feeding, ever			
Breast-feeding, ever (yes)			
Units: Subjects			
Breast-feeding, ever (yes)	68	38	106
No breastfeeding or no data	13	2	15
Tympanostomy			
Tympanostomy, ever			
Units: Subjects			

Tympanostomy, ever	12	6	18
No tympanostomy or no data	69	34	103

Pacifier use			
Pacifier use duration			
Units: Months			
arithmetic mean	16	11	
standard deviation	± 12	± 11	-
Number of siblings			
Units: Number of siblings			
arithmetic mean	2.0	1.2	
standard deviation	± 2.7	± 1.2	-
Siblings' AOM			
Siblings' AOM, number of			
Units: Number of			
arithmetic mean	4.2	4.0	
standard deviation	± 6.7	± 7.1	-
Total previous courses of systemic antibiotics			
Total previous courses of systemic antibiotics			
Units: Number of			
arithmetic mean	2.8	4.1	
standard deviation	± 2.9	± 5.6	-
Duration of daycare, months			
Units: Months			
arithmetic mean	22	18	
standard deviation	± 14	± 15	-
Breast-feeding			
Breast-feeding duration			
Units: Months			
arithmetic mean	10	9.6	
standard deviation	± 6.9	± 5.1	-
Tympanostomy, at recruitment			
Units: Subjects with tympanostomy tubes present			
arithmetic mean	1	2	
standard deviation	± 1.2	± 5.0	-
Parental smoking			
Parental smoking (yes, %)			
Units: percent			
arithmetic mean	19	10	
standard deviation	± 39	± 31	-

End points

End points reporting groups	
Reporting group title	Streptococcus salivarius K12
Reporting group description: S. salivarius K12 oral soluble powder or tablet for 30 days	
Reporting group title	No treatment
Reporting group description: -	
Reporting group title	Streptococcus salivarius K12
Reporting group description: -	
Reporting group title	No treatment
Reporting group description: -	
Reporting group title	Streptococcus salivarius K12
Reporting group description: S. salivarius treatment, ended	
Reporting group title	No treatment
Reporting group description: No treatment, follow-up	

Primary: Recruitment nasopharyngeal relat. abund.	
End point title	Recruitment nasopharyngeal relat. abund.
End point description: Nasopharyngeal	
End point type	Primary
End point timeframe: Upon recruitment	

End point values	Streptococcus salivarius K12	No treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58[1]	27		
Units: percent				
arithmetic mean (standard deviation)				
Actinobacteria	8.3 (± 16)	14 (± 23)		
Bacteroidetes	9.3 (± 15)	3.6 (± 4.1)		
Firmicutes	56 (± 29)	58 (± 27)		
Fusobacteria	0.3 (± 1.1)	0.4 (± 0.8)		
Proteobacteria	25 (± 30)	24 (± 22)		

Notes:
[1] - 27

Statistical analyses

Statistical analysis title	Actinobacteria
Comparison groups	Streptococcus salivarius K12 v No treatment

Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
sides	2-sided
lower limit	-4.1
upper limit	16

Statistical analysis title	Bacteroidetes
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.9
upper limit	1.6

Statistical analysis title	Firmicutes
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11
upper limit	15

Statistical analysis title	Fusobacteria
Comparison groups	Streptococcus salivarius K12 v No treatment

Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	0.4

Statistical analysis title	Proteobacteria
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14
upper limit	12

Primary: Recruitment diversity nasopharynx

End point title	Recruitment diversity nasopharynx
End point description:	

End point type	Primary
End point timeframe:	
Recruitment	

End point values	Streptococcus salivarius K12	No treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	27		
Units: percent				
arithmetic mean (standard deviation)				
Shannon index	2.6 (± 1.2)	2.4 (± 1.0)		
Observed OTUs	21 (± 9.2)	25 (± 13)		
Faith index	2.6 (± 1.1)	2.4 (± 0.8)		

Statistical analyses

Statistical analysis title	Faith index
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.2

Statistical analysis title	Shannon index
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.3

Statistical analysis title	Observed OTUs
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.5
upper limit	1.4

Primary: Study np relative abundance

End point title	Study np relative abundance
End point description:	
Nasopharynx	
End point type	Primary
End point timeframe:	
After 1 month use S. salivarius K12 or no treatment	

End point values	Streptococcus salivarius K12	No treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	22		
Units: percent				
arithmetic mean (standard deviation)				
Actinobacteria	8.3 (± 16)	10 (± 18)		
Bacteroidetes	8.2 (± 12)	2.4 (± 3.3)		
Firmicutes	56 (± 28)	51 (± 35)		
Fusobacteria	0.5 (± 1.2)	0.2 (± 0.4)		
Proteobacteria	25 (± 30)	35 (± 38)		

Statistical analyses

Statistical analysis title	Actinobacteria
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.4
upper limit	11

Statistical analysis title	Bacteroidetes
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.9
upper limit	1.7

Statistical analysis title	Firmicutes
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22
upper limit	11

Statistical analysis title	Fusobacteria
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	1.1

Statistical analysis title	Proteobacteria
Comparison groups	Streptococcus salivarius K12 v No treatment

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.5
upper limit	28

Primary: Study saliva relative abundance

End point title	Study saliva relative abundance

End point description:

End point type	Primary

End point timeframe:

After 1 month use of S. salivarius K12 or no treatment

End point values	Streptococcus salivarius K12	No treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	32		
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	20 (± 12)	24 (± 12)		
Firmicutes	61 (± 18)	58 (± 16)		
Fusobacteria	2.8 (± 4.8)	2.8 (± 2.5)		
Proteobacteria	13 (± 11)	14 (± 8.8)		

Statistical analyses

Statistical analysis title	Bacteroidetes
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.09

Statistical analysis title	Firmicutes
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11
upper limit	4.7

Statistical analysis title	Fusobacteria
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	1.8

Statistical analysis title	Proteobacteria
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	5.2

Primary: Recruitment saliva relat. abund.

End point title	Recruitment saliva relat. abund.
End point description:	

End point type	Primary
End point timeframe:	
Recruitment	

End point values	Streptococcus salivarius K12	No treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	34		
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	28 (± 12)	26 (± 13)		
Firmicutes	52 (± 15)	54 (± 15)		
Fusobacteria	4.2 (± 3.7)	3.8 (± 2.7)		
Proteobacteria	14 (± 9.9)	14 (± 8.5)		

Statistical analyses

Statistical analysis title	Relative abundance of Bacteroidetes
Comparison groups	No treatment v Streptococcus salivarius K12
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.9
upper limit	3.3
Variability estimate	Standard deviation

Statistical analysis title	Firmicutes
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	8.5

Statistical analysis title	Fusobacteria
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	1

Statistical analysis title	Proteobacteria
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	3.7

Primary: Recruitment saliva diversity

End point title	Recruitment saliva diversity

End point description:

End point type	Primary

End point timeframe:

Recruitment

End point values	Streptococcus salivarius K12	No treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	34		
Units: percent				
arithmetic mean (standard deviation)				
Observed OTUs	44 (± 13)	48 (± 15)		
Shannon index	4.0 (± 0.6)	4.2 (± 0.6)		
Faith index	4.0 (± 0.8)	4.2 (± 0.8)		

Statistical analyses

Statistical analysis title	Observed OTUs
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	9.9

Statistical analysis title	Shannon index
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference

Confidence interval	
level	95 %
sides	2-sided
lower limit	-11
upper limit	36

Statistical analysis title	Faith index
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12
upper limit	52

Primary: Study np diversity

End point title	Study np diversity

End point description:

End point type	Primary

End point timeframe:

After 1 month use of S. saliavrtius K12 or no treatment

End point values	Streptococcus salivarius K12	No treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	22		
Units: percent				
arithmetic mean (standard deviation)				
Observed OTUs	23 (± 12)	20 (± 10)		
Shannon index	2.7 (± 1.2)	2.1 (± 1.2)		
Faith index	2.5 (± 1.1)	2.2 (± 1.1)		

Statistical analyses

Statistical analysis title	Observed OTUs
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.1
upper limit	3.1

Statistical analysis title	Shannon index
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	0.1

Statistical analysis title	Faith index
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.4

Primary: Study saliva diversity

End point title	Study saliva diversity
End point description: saliva	
End point type	Primary
End point timeframe: After 1 month of S. salivarius K12 or no treatment	

End point values	Streptococcus salivarius K12	No treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	32		
Units: percent				
arithmetic mean (standard deviation)				
Observed OTUs	37 (± 14)	39 (± 14)		
Shannon index	3.8 (± 0.6)	3.9 (± 0.5)		
Faith index	3.6 (± 0.9)	3.7 (± 0.9)		

Statistical analyses

Statistical analysis title	Observed OTUs
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	8.9

Statistical analysis title	Shannon index
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.6
upper limit	43

Statistical analysis title	Faith index
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12
upper limit	52

Primary: Follow-up np relat. abundance
End point title: Follow-up np relat. abundance
End point description: nasopharyngeal
End point type: Primary
End point timeframe: 1 month after stopping the study product

End point values	Streptococcus salivarius K12	No treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	13		
Units: percent				
arithmetic mean (standard deviation)				
Actinobacteria	9.5 (± 14)	3.0 (± 3.7)		
Bacteroidetes	6.4 (± 10)	7.9 (± 15)		
Firmicutes	54 (± 29)	44 (± 35)		
Fusobacteria	0.3 (± 0.6)	0.7 (± 1.2)		
Proteobacteria	29 (± 30)	44 (± 37)		

Statistical analyses

Statistical analysis title	Actinobacteria
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12
upper limit	1.4

Statistical analysis title	Bacteroidetes
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.9
upper limit	9

Statistical analysis title	Firmicutes
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29
upper limit	9.9

Statistical analysis title	Fusobacteria

Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.1

Statistical analysis title	Proteobacteria
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	35

Primary: Follow-up saliva relat. abundance

End point title	Follow-up saliva relat. abundance
End point description: saliva	
End point type	Primary
End point timeframe: 2 months from recruitment (1 month after study product or no treatment stopping)	

End point values	Streptococcus salivarius K12	No treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	24		
Units: percent				
arithmetic mean (standard deviation)				
Bacteroidetes	23 (± 12)	27 (± 14)		
Firmicutes	57 (± 15)	54 (± 15)		
Fusobacteria	2.8 (± 2.5)	3.7 (± 3.2)		

Proteobacteria	16 (± 14)	14 (± 7.3)		

Statistical analyses

Statistical analysis title	Bacteroidetes
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	10

Statistical analysis title	Firmicutes
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11
upper limit	3.8

Statistical analysis title	Fusobacteria
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	2.2

Statistical analysis title	Proteobacteria
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.7
upper limit	4.1

Primary: Follow-up np diversity

End point title	Follow-up np diversity

End point description:

End point type	Primary

End point timeframe:

2 months from recruitment (1 month after stopping study product or no treatment)

End point values	Streptococcus salivarius K12	No treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	13		
Units: percent				
arithmetic mean (standard deviation)				
Observed OTUs	25 (± 11)	28 (± 12)		
Shannon index	2.6 (± 1.1)	2.4 (± 1.3)		
Faith index	2.7 (± 1.0)	2.7 (± 0.9)		

Statistical analyses

Statistical analysis title	Observed OTUs
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	10

Statistical analysis title	Shannon index
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.6

Statistical analysis title	Faith index
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.7

Primary: Follow-up saliva diversity

End point title	Follow-up saliva diversity

End point description:

End point type	Primary

End point timeframe:

2 months after recruitment (1 month after stopping study product use or no treatment)

End point values	Streptococcus salivarius K12	No treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	24		
Units: percent				
arithmetic mean (standard deviation)				
Observed OTUs	39 (± 13)	43 (± 13)		
Shannon index	3.8 (± 0.7)	3.9 (± 0.6)		
Faith index	3.7 (± 0.7)	3.8 (± 0.7)		

Statistical analyses

Statistical analysis title	Observed OTUs
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	10

Statistical analysis title	Shannon index
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference

Confidence interval	
level	95 %
sides	2-sided
lower limit	-19
upper limit	46

Statistical analysis title	Faith index
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19
upper limit	51

Secondary: Recruitment nasopharyngeal s. salivarius abundance

End point title	Recruitment nasopharyngeal s. salivarius abundance[2]

End point description:

End point type	Secondary

End point timeframe:

Recruitment

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The outcome was the change of S. salivarius abundance in those receiving active treatment, so the baseline needs to be reported as well.

End point values	Streptococcus salivarius K12			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: percent				
arithmetic mean (standard deviation)				
Streptococcus salivarius	1.9 (± 5.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Recruitment saliva s. salivarius abundance

End point title	Recruitment saliva s. salivarius abundance[3]

End point description:

End point type	Secondary

End point timeframe:

recruitment

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The outcome was the change of S. salivarius abundance in those receiving active treatment, so the baseline needs to be reported as well.

End point values	Streptococcus salivarius K12			
Subject group type	Reporting group			
Number of subjects analysed	69			
Units: percent				
arithmetic mean (standard deviation)				
Streptococcus salivarius	0.9 (± 1.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Study period nasopharyngeal s. salivarius abundance

End point title	Study period nasopharyngeal s. salivarius abundance

End point description:

End point type	Secondary

End point timeframe:

After 1 month use of study product or no treatment

End point values	Streptococcus salivarius K12			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: percent				
arithmetic mean (standard deviation)				
S. salivarius	2.0 (± 2.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Study period saliva s. salivarius abundance

End point title	Study period saliva s. salivarius abundance

End point description:

End point type	Secondary

End point timeframe:

After 1 month use of study prodict or no treatment

End point values	Streptococcus salivarius K12			
Subject group type	Reporting group			
Number of subjects analysed	52			
Units: percent				
arithmetic mean (standard deviation)				
S. salivarius	2.0 (± 2.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Follow-up period nasopharyngeal s. salivarius abundance

End point title	Follow-up period nasopharyngeal s. salivarius abundance

End point description:

End point type	Secondary

End point timeframe:

2 months from recruitment (1 month after stopping study product or no treatment)

End point values	Streptococcus salivarius K12			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: percent				
arithmetic mean (standard deviation)				
S. salivarius	0.7 (± 0.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Follow-up period saliva s. salivarius abundance

End point title	Follow-up period saliva s. salivarius abundance

End point description:

End point type	Secondary

End point timeframe:

2 months from recruitment (1 month after stopping study product or no treatment)

End point values	Streptococcus salivarius K12			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: percent				
arithmetic mean (standard deviation)				
S. salivarius	0.8 (± 1.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Recruitment proportion of children with otopathogen in nasopharyngeal microbiome

End point title	Recruitment proportion of children with otopathogen in nasopharyngeal microbiome

End point description:

End point type	Secondary

End point timeframe:

Recruitment

End point values	Streptococcus salivarius K12	No treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	40		
Units: percent				
number (not applicable)				
Streptococcus pneumoniae	50	48		
Streptococcus pyogenes	17	19		
Moraxella	90	100		
Haemophilus influenzae	22	19		
Any otopathogen	91	100		

Statistical analyses

Statistical analysis title	S. pneumoniae
Comparison groups	No treatment v Streptococcus salivarius K12
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24
upper limit	20
Variability estimate	Standard deviation

Notes:

[4] - S. pneumoniae

Statistical analysis title	S. pyogenes
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15
upper limit	21
Variability estimate	Standard deviation

Statistical analysis title	Moraxella
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
sides	2-sided
lower limit	-2.6
upper limit	21
Variability estimate	Standard deviation

Statistical analysis title	H. influenzae
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21
upper limit	17
Variability estimate	Standard deviation

Statistical analysis title	Any otopathogen
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	19
Variability estimate	Standard deviation

Secondary: 1 month proportion of children with otopathogen in nasopharyngeal microbiome

End point title	1 month proportion of children with otopathogen in nasopharyngeal microbiome
End point description:	

End point type	Secondary
End point timeframe:	
1 month	

End point values	Streptococcus salivarius K12	No treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	40		
Units: percent				
number (not applicable)				
S. pneumoniae	37	36		
S. pyogenes	21	14		
Moraxella	82	86		
H. influenzae	32	27		
Any otopathogen	95	96		

Statistical analyses

Statistical analysis title	S. pneumoniae
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24
upper limit	25
Variability estimate	Standard deviation

Statistical analysis title	S. pyogenes
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26
upper limit	15

Statistical analysis title	Moraxella

Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17
upper limit	24

Statistical analysis title	H. influenzae
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27
upper limit	21

Statistical analysis title	Any otopathogen
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
sides	2-sided
lower limit	-17
upper limit	14

Secondary: Follow-up proportion of children with otopathogen in nasopharyngeal microbiome

End point title	Follow-up proportion of children with otopathogen in nasopharyngeal microbiome

End point description:

End point type	Secondary

End point timeframe:

1 mo after stopping intervention

End point values	Streptococcus salivarius K12	No treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	40		
Units: persons				
S. pneumoniae	57	39		
S. pyogenes	11	31		
Moraxella	87	100		
H. influenzae	19	15		
Any otopathogen	89	100		

Statistical analyses

Statistical analysis title	S. pneumoniae
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-45
upper limit	13

Statistical analysis title	S. pyogenes
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference

Confidence interval	
sides	2-sided
lower limit	-3
upper limit	49

Statistical analysis title	Moraxella
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	11
upper limit	28

Statistical analysis title	H. influenzae
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14
upper limit	25

Statistical analysis title	Any otopathogen
Comparison groups	No treatment v Streptococcus salivarius K12
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference

Confidence interval	
level	95 %
sides	2-sided
lower limit	-14
upper limit	25

Secondary: Use of other probiotic product

End point title	Use of other probiotic product

End point description:

Number of subjects who reported that they used other probiotic products during the study period (1 month from recruitment to stopping the study product)

End point type	Secondary

End point timeframe:

During the entire study

End point values	Streptococcus salivarius K12	No treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	38		
Units: subjects				
Any other probiotic product	15	17		

Statistical analyses

Statistical analysis title	Use of probiotic products
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.058
Method	t-test, 2-sided

Secondary: Feasibility of oral powder, liked the product

End point title	Feasibility of oral powder, liked the product

End point description:

"Did you like the study product overall? Likert score 4 or more (1 to 5, 5=agree strongly, 4=agree, 3=no opinion, 2=disagree, 1=strongly disagree)

End point type	Secondary

End point timeframe:

Study period, during the use of study product

End point values	Streptococcus salivarius K12			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percent				
number (not applicable)	82			

Statistical analyses

No statistical analyses for this end point

Secondary: Use of antibiotics during the study

End point title	Use of antibiotics during the study

End point description:

End point type	Secondary

End point timeframe:

During the intervention

End point values	Streptococcus salivarius K12	No treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	40		
Units: mean number of antibiotic courses				
arithmetic mean (standard deviation)	0.1 (± 0.30)	0.06 (± 0.23)		

Statistical analyses

Statistical analysis title	Antibiotic courses
Comparison groups	Streptococcus salivarius K12 v No treatment
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.37
Method	t-test, 2-sided
Parameter estimate	95% CI of the difference

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.05

Secondary: Feasibility of chewing tablet, liked the product

End point title	Feasibility of chewing tablet, liked the product

End point description:

"Did you like the study product overall? Likert score 4 or more (1 to 5, 5=agree strongly, 4=agree, 3=no opinion, 2=disagree, 1=strongly disagree)

End point type	Secondary

End point timeframe:

During the study

End point values	Streptococcus salivarius K12			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: percent				
number (not applicable)	84			

Statistical analyses

No statistical analyses for this end point

Secondary: Study product taste oral powder

End point title	Study product taste oral powder

End point description:

"I liked the study product taste? Likert score 4 or more (1 to 5, 5=agree strongly, 4=agree, 3=no opinion, 2=disagree, 1=strongly disagree)

End point type	Secondary

End point timeframe:

During the study period

End point values	Streptococcus salivarius K12			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percent				
number (not applicable)	94			

Statistical analyses

No statistical analyses for this end point

Secondary: Study product taste chewing tablet

End point title	Study product taste chewing tablet

End point description:

"Did you like the study product taste? Likert score 4 or more (1 to 5, 5=agree strongly, 4=agree, 3=no opinion, 2=disagree, 1=strongly disagree)

End point type	Secondary

End point timeframe:

During the styudy period

End point values	Streptococcus salivarius K12			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: percent				
number (not applicable)	77			

Statistical analyses

No statistical analyses for this end point

Secondary: Oral powder easy to use

End point title	Oral powder easy to use

End point description:

End point type	Secondary

End point timeframe:

"Did you like the study product easy to use? Likert score 4 or more (1 to 5, 5=agree strongly, 4=agree, 3=no opinion, 2=disagree, 1=strongly disagree)

End point values	Streptococcus salivarius K12			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percent				
number (not applicable)	61			

Statistical analyses

No statistical analyses for this end point

Secondary: Chewing tablet easy to use

End point title	Chewing tablet easy to use

End point description:

"Did you like the study product easy to use? Likert score 4 or more (1 to 5, 5=agree strongly, 4=agree, 3=no opinion, 2=disagree, 1=strongly disagree) Likert score 4 or more

End point type	Secondary

End point timeframe:

During the study period

End point values	Streptococcus salivarius K12			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: percent				
number (not applicable)	87			

Statistical analyses

No statistical analyses for this end point

Secondary: Daily use oral powder

End point title	Daily use oral powder

End point description:

Yes or no / answered yes

End point type	Secondary

End point timeframe:

During the study period

End point values	Streptococcus salivarius K12			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: percent				
number (not applicable)	88			

Statistical analyses

No statistical analyses for this end point

Secondary: Daily use of tablet

End point title	Daily use of tablet

End point description:

Did you use the study product daily? Yes/no, answered yes

End point type	Secondary

End point timeframe:

During the study

End point values	Streptococcus salivarius K12			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: percent				
number (not applicable)	81			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 2 months - from baseline to follow up visit	
Assessment type	Systematic
Dictionary used	
Dictionary name	None
Dictionary version	0
Reporting groups	
Reporting group title	S. salivarius K12
Reporting group description: From recruitment to 2 month post recruitment	

Serious adverse events	S. salivarius K12		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 81 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	S. salivarius K12		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 81 (3.70%)		
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: Cough during taking the study product		
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Growing pains			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Infections and infestations			
Viral infection	Additional description: Multiple infections suspected viral		
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 November 2017	Some adjustuments in the wording of the EudraCT sheet were made. Viral analysis and FISH analysis were omitted in the amendment. Webropol questionnaires 6 and 12 months post recruitment were removed from the study protocol during the study. The primary and secondary outcomes were met during the 2 month study period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33298762