



## Clinical trial results:

### Placebo controlled study on effects of vitamin D supplementation in type 1 diabetic subjects on immunological, endocrine and metabolic parameters: Step 2 of the Austrian Diabetes Prevention Programme (ADPP-002)

#### Summary

EudraCT number	2010-018901-12
Trial protocol	AT
Global end of trial date	27 January 2014

#### Results information

Result version number	v1 (current)
This version publication date	06 August 2021
First version publication date	06 August 2021

#### Trial information

##### Trial identification

Sponsor protocol code	ADPP-002ENM-DA-017
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01390480
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Medical University of Graz, Department of Internal Medicine, Division of Endocrinology and Diabetology, Austria
Sponsor organisation address	Auenbruggerplatz 15, Graz, Austria, 8036
Public contact	Co-investigator: Gerlies Treiber, Medical University of Graz, gerlies.treiber@medunigraz.at
Scientific contact	Principal Investigators: Thomas R. Pieber and Martin Borkenstein, Medical University of Graz, thomas.pieber@medunigraz.at

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:

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**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	16 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 September 2013
Global end of trial reached?	Yes
Global end of trial date	27 January 2014
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

Main objective of the trial:

To evaluate whether vitamin D supplementation significantly alters the proportion of circulating CD4+ T cells in subjects with type 1 diabetes (T1D)

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice. All study participants were required to give written informed consent before any trial-related activities were initiated. Informed consent was either given by the participants or their guardians and in addition, assent from all children was obtained.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 November 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	Austria: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

Notes:

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**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)	11
Adolescents (12-17 years)	13
Adults (18-64 years)	6
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Recruitment was performed in three diabetes outpatient clinics in Austria (Graz, Vienna and Salzburg).

### Pre-assignment

Screening details:

A total of 31 participants were screened and 30 were enrolled and randomly allocated in a 1:1 ratio to the treatment or placebo group. Out of these, 29 participants (treatment group n=14, placebo group n=15) completed the trial. Only the completers were included in the analysis.

### Period 1

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

Blinding implementation details:

The random allocation sequence was provided by staff with no other involvement in the trial. Unblinded trial staff ensured the correct treatment allocation and dispensing of trial products. Trial products were filled by an independent pharmacy and sent blinded to the study centres. They were visually identical, and were packed and labelled to fulfil the requirements for double-blind procedures.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Treatment group

Arm description:

The trial consisted of 14 visits (a baseline visit, study visits after 1, 3, 6, 9 and 12 months, a follow-up visit after 13 months and regular telephone visits in between).

In the first month of treatment a loading dose of 140 IU cholecalciferol/kg body weight/day was administered to achieve serum vitamin D (25(OH)D) levels in the upper normal range. Oleovit D3 Tropfen (vitamin D drops, 400 IU/drop) was given orally once weekly. Compliance was assessed by phone contacts and the participant's study diaries.

15 participants have been allocated to the treatment group. One participant of the treatment group was excluded after 3 months due to intentional additional intake of vitamin D supplementation and all data from this participant were excluded from analysis.

Arm type	Experimental
Investigational medicinal product name	OLEOVIT D3 Tropfen (Fresenius Kabi, Austria)
Investigational medicinal product code	10.989
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

Oleovit D3 drops, oral administration; 140 IU cholecalciferol/kg body weight/day in the first month followed by 70 IU cholecalciferol/kg body weight/day; the dose was weight-adjusted once weekly.

<b>Arm title</b>	Placebo group
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Arm description:

The trial consisted of 14 visits (a baseline visit, study visits after 1, 3, 6, 9 and 12 months, a follow-up visit after 13 months and regular telephone visits in between).

Placebo (peanut oil) was given orally once weekly. Compliance was assessed by phone contacts and the participant's study diaries.

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

Dosage and administration details:

Peanut oil suspension, oral administration, amount equal to Oleovit D3 Tropfen.

<b>Number of subjects in period 1<sup>[1]</sup></b>	Treatment group	Placebo group
Started	14	15
Completed	14	15

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: One participant of the treatment group was excluded after 3 months due to intentional additional intake of vitamin D supplementation and all data from this participant were excluded from analysis.

## Baseline characteristics

### Reporting groups

Reporting group title	Treatment group
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Reporting group description:

The trial consisted of 14 visits (a baseline visit, study visits after 1, 3, 6, 9 and 12 months, a follow-up visit after 13 months and regular telephone visits in between).

In the first month of treatment a loading dose of 140 IU cholecalciferol/kg body weight/day was administered to achieve serum vitamin D (25(OH)D) levels in the upper normal range. Oleovit D3 Tropfen (vitamin D drops, 400 IU/drop) was given orally once weekly. Compliance was assessed by phone contacts and the participant's study diaries.

15 participants have been allocated to the treatment group. One participant of the treatment group was excluded after 3 months due to intentional additional intake of vitamin D supplementation and all data from this participant were excluded from analysis.

Reporting group title	Placebo group
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Reporting group description:

The trial consisted of 14 visits (a baseline visit, study visits after 1, 3, 6, 9 and 12 months, a follow-up visit after 13 months and regular telephone visits in between).

Placebo (peanut oil) was given orally once weekly. Compliance was assessed by phone contacts and the participant's study diaries.

Reporting group values	Treatment group	Placebo group	Total
Number of subjects	14	15	29
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)	5	5	10
Adolescents (12-17 years)	5	8	13
Adults (18-64 years)	4	2	6
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
median	12	13	
inter-quartile range (Q1-Q3)	11.0 to 17.5	9.5 to 15.5	-
Gender categorical			
Units: Subjects			
Female	3	4	7
Male	11	11	22
Body weight			
Units: kg			
arithmetic mean	52.2	44.0	
standard deviation	± 21.0	± 14.4	-
Body mass index			
Units: kg/m <sup>2</sup>			
arithmetic mean	19.2	17.4	
standard deviation	± 3.8	± 2.1	-

Diabetes duration			
Units: days			
arithmetic mean	61	61	
standard deviation	± 20	± 28	-
HbA1c			
Units: mmol/mol			
arithmetic mean	54.5	63.5	
standard deviation	± 11.6	± 16.1	-

## End points

### End points reporting groups

Reporting group title	Treatment group
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Reporting group description:

The trial consisted of 14 visits (a baseline visit, study visits after 1, 3, 6, 9 and 12 months, a follow-up visit after 13 months and regular telephone visits in between).

In the first month of treatment a loading dose of 140 IU cholecalciferol/kg body weight/day was administered to achieve serum vitamin D (25(OH)D) levels in the upper normal range. Oleovit D3 Tropfen (vitamin D drops, 400 IU/drop) was given orally once weekly. Compliance was assessed by phone contacts and the participant's study diaries.

15 participants have been allocated to the treatment group. One participant of the treatment group was excluded after 3 months due to intentional additional intake of vitamin D supplementation and all data from this participant were excluded from analysis.

Reporting group title	Placebo group
-----------------------	---------------

Reporting group description:

The trial consisted of 14 visits (a baseline visit, study visits after 1, 3, 6, 9 and 12 months, a follow-up visit after 13 months and regular telephone visits in between).

Placebo (peanut oil) was given orally once weekly. Compliance was assessed by phone contacts and the participant's study diaries.

### Primary: Changes in number and function of regulatory T cells

End point title	Changes in number and function of regulatory T cells
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End point description:

End point type	Primary
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End point timeframe:

Months 0, 3, 6 and 12 of treatment

End point values	Treatment group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	15		
Units: Percent				
arithmetic mean (standard deviation)				
Tregs in CD4, 0 months	6.1 ( $\pm$ 1.9)	4.8 ( $\pm$ 1.7)		
Tregs in CD4, 3 months	5.6 ( $\pm$ 0.8)	5.1 ( $\pm$ 1.5)		
Tregs in CD4, 6 months	5.7 ( $\pm$ 1.4)	5.8 ( $\pm$ 1.8)		
Tregs in CD4, 12 months	5.8 ( $\pm$ 1.5)	5.4 ( $\pm$ 1.7)		
Suppression of Teffs, 0 months	-1.6 ( $\pm$ 25.6)	19.7 ( $\pm$ 26.7)		
Suppression of Teffs, 3 months	30.5 ( $\pm$ 39.4)	35.1 ( $\pm$ 23.3)		
Suppression of Teffs, 6 months	44.6 ( $\pm$ 23.8)	25.8 ( $\pm$ 24.8)		
Suppression of Teffs, 12 months	37.2 ( $\pm$ 25.0)	0.7 ( $\pm$ 28.9)		

### Statistical analyses

<b>Statistical analysis title</b>	Statistical analysis
Statistical analysis description:	
Data were checked for normality by using Shapiro-Wilk test. Data that were not normally distributed were log transformed for analysis. Data were analysed with two-way repeated-measures ANOVA to determine changes over 12 months. Student's t-test was applied to compare differences between the groups. Mann-Whitney U-test was used for group comparisons if data deviated from normality. For the primary end point, the Bonferroni-Holm procedure was used to maintain an overall type 1 error rate of 5%.	
Comparison groups	Treatment group v Placebo group
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	ANOVA

### Secondary: Effect on apoptosis of Tregs and Teffs

End point title	Effect on apoptosis of Tregs and Teffs
End point description:	
End point type	Secondary
End point timeframe:	
Months 0, 3, 6 and 12 of treatment	

End point values	Treatment group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Percent				
arithmetic mean (standard deviation)				
Apoptotic cells within Tregs, 0 months	4.6 (± 4.9)	2.4 (± 2.7)		
Apoptotic cells within Tregs, 3 months	1.2 (± 1.7)	0.9 (± 0.8)		
Apoptotic cells within Tregs, 6 months	2.4 (± 1.8)	1.4 (± 0.6)		
Apoptotic cells within Tregs, 12 months	1.2 (± 0.7)	1.8 (± 0.7)		
Apoptotic cells within Teffs, 0 months	2.2 (± 1.5)	2.4 (± 2.6)		
Apoptotic cells within Teffs, 3 months	1.0 (± 0.9)	1.9 (± 1.3)		
Apoptotic cells within Teffs, 6 months	2.6 (± 1.8)	1.5 (± 1.6)		
Apoptotic cells within Teffs, 12 months	2.1 (± 1.2)	0.8 (± 0.4)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Effect on endogenous insulin production

End point title	Effect on endogenous insulin production
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End point description:

End point type	Secondary
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End point timeframe:

Months 0, 6 and 12 of treatment

End point values	Treatment group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	13		
Units: nmol/L				
arithmetic mean (standard deviation)				
Fasting C-peptide, 0 months	0.20 (± 0.06)	0.21 (± 0.09)		
Fasting C-peptide, 6 months	0.18 (± 0.11)	0.15 (± 0.08)		
Fasting C-peptide, 12 months	0.20 (± 0.11)	0.12 (± 0.07)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Effect on HbA1c

End point title	Effect on HbA1c
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End point description:

End point type	Secondary
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End point timeframe:

Months 0, 3, 6 and 12 of treatment

End point values	Treatment group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	15		
Units: mmol/mol				
arithmetic mean (standard deviation)				
HbA1c, 0 months	54.5 (± 11.6)	63.5 (± 16.1)		
HbA1c, 3 months	46.9 (± 10.2)	50.5 (± 12.4)		
HbA1c, 6 months	50.4 (± 15.0)	54.2 (± 17.7)		
HbA1c, 12 months	55.9 (± 16.2)	55.3 (± 12.3)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Effect on insulin requirement

End point title Effect on insulin requirement

End point description:

End point type Secondary

End point timeframe:

Months 0, 3, 6 and 12 of treatment

End point values	Treatment group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	15		
Units: IU/kg body weight/day				
arithmetic mean (standard deviation)				
Insulin, 0 months	0.45 (± 0.19)	0.46 (± 0.22)		
Insulin, 3 months	0.37 (± 0.14)	0.39 (± 0.20)		
Insulin, 6 months	0.42 (± 0.23)	0.42 (± 0.22)		
Insulin, 12 months	0.45 (± 0.22)	0.64 (± 0.22)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Effect on serum 25(OH)D

End point title Effect on serum 25(OH)D

End point description:

End point type Secondary

End point timeframe:

Months 0, 3, 6 and 12 of treatment

End point values	Treatment group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	15		
Units: nmol/L				
arithmetic mean (standard deviation)				
Serum 25(OH)D, 0 months	59.2 (± 20.0)	77.1 (± 39.9)		
Serum 25(OH)D, 3 months	159.5 (± 39.4)	82.1 (± 55.4)		
Serum 25(OH)D, 6 months	166.2 (± 28.2)	83.9 (± 30.2)		
Serum 25(OH)D, 12 months	154.0 (± 68.4)	80.1 (± 43.4)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Effect on serum calcium

End point title	Effect on serum calcium
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End point description:

End point type	Secondary
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End point timeframe:

Months 0, 3, 6 and 12 of treatment

End point values	Treatment group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	15		
Units: mmol/L				
arithmetic mean (standard deviation)				
Serum calcium, 0 months	2.38 (± 0.10)	2.43 (± 0.07)		
Serum calcium, 3 months	2.40 (± 0.09)	2.42 (± 0.10)		
Serum calcium, 6 months	2.42 (± 0.11)	2.42 (± 0.09)		
Serum calcium, 12 months	2.42 (± 0.10)	2.43 (± 0.09)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Effect on serum parathormone

End point title	Effect on serum parathormone
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End point description:

End point type	Secondary
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End point timeframe:

Months 0, 3, 6 and 12 of treatment

End point values	Treatment group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	7		
Units: pg/mL				
arithmetic mean (standard deviation)				
Parathormone, 0 months	37.7 (± 10.9)	39.1 (± 15.2)		
Parathormone, 3 months	26.8 (± 10.2)	34.6 (± 10.3)		
Parathormone, 6 months	32.6 (± 16.9)	46.9 (± 14.8)		
Parathormone, 12 months	33.9 (± 18.0)	42.0 (± 18.1)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Effect on urine calcium/creatinine ratio

End point title	Effect on urine calcium/creatinine ratio
End point description:	
End point type	Secondary
End point timeframe:	
Months 0, 3, 6 and 12 of treatment	

End point values	Treatment group	Placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	11		
Units: Ratio				
arithmetic mean (standard deviation)				
Urine calcium/creatinine ratio, 0 months	0.20 (± 0.16)	0.29 (± 0.17)		
Urine calcium/creatinine ratio, 3 months	0.41 (± 0.37)	0.32 (± 0.24)		
Urine calcium/creatinine ratio, 6 months	0.40 (± 0.36)	0.30 (± 0.29)		
Urine calcium/creatinine ratio, 12 months	0.36 (± 0.28)	0.20 (± 0.13)		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All adverse events were collected from written informed consent up to the follow-up visit, regardless of seriousness or relationship to the trial products.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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### Reporting groups

Reporting group title	Treatment group
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Reporting group description: -

Reporting group title	Placebo group
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Reporting group description: -

Serious adverse events	Treatment group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 14 (14.29%)	2 / 15 (13.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Enteritis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Insulin therapy	Additional description: Hospitalisation due to initiation of an insulin pump		
subjects affected / exposed	1 / 14 (7.14%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Non-serious adverse events	Treatment group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 14 (50.00%)	10 / 15 (66.67%)	
Injury, poisoning and procedural complications			
Ligament rupture			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Foot fracture	Additional description: Broken metatarsal		
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Fracture	Additional description: Osseous tear fibula distal		
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Skin abrasion			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Ligament sprain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Hand fracture			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 14 (14.29%)	1 / 15 (6.67%)	
occurrences (all)	2	1	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 14 (7.14%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	0 / 14 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Psychiatric disorders			
Persistent depressive disorder			

subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 15 (6.67%) 1	
Renal and urinary disorders Nephrocalcinosis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 15 (6.67%) 1	
Endocrine disorders Insulin therapy subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 15 (6.67%) 1	
Infections and infestations Gingivitis subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 15 (0.00%) 0	
Rhinitis subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2	1 / 15 (6.67%) 2	
Tonsillitis subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	1 / 15 (6.67%) 1	
Otitis media subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1	0 / 15 (0.00%) 0	
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 15 (6.67%) 1	
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	2 / 15 (13.33%) 2	
Respiratory tract infection subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 15 (6.67%) 1	
Impetigo subjects affected / exposed occurrences (all)	0 / 14 (0.00%) 0	1 / 15 (6.67%) 1	
Influenza			

subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26277548>