



## Clinical trial results:

### - PRE-POINT-EARLY STUDY -

## Pilot study using oral insulin at early age for immune efficacy in primary prevention of type 1 diabetes

### Summary

EudraCT number	2014-005287-15
Trial protocol	DE
Global end of trial date	21 December 2017

### Results information

Result version number	v1 (current)
This version publication date	22 August 2020
First version publication date	22 August 2020

### Trial information

#### Trial identification

Sponsor protocol code	808040017
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02547519
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Technische Universität München; Fakultät für Medizin
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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	21 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 December 2017
Global end of trial reached?	Yes
Global end of trial date	21 December 2017
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

Main objective of the trial:

To determine whether daily administration of up to 67.5 mg insulin to young children aged 6 months to 2 years with high genetic risk for T1D induces immune responses to insulin with features of immune regulation.

Protection of trial subjects:

Local anesthetics (EMLA) to reduce pain during blood draws

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 December 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects****Subjects enrolled per country**

Country: Number of subjects enrolled	Germany: 44
Worldwide total number of subjects	44
EEA total number of subjects	44

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)	38
Children (2-11 years)	6
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: -

### Pre-assignment

Screening details:

Children from age 6 months to 2 years who have at least one first degree relative with type 1 diabetes diagnosed before age 40 years.

### 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, Data analyst, Carer, Assessor

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Oral Insulin

Arm description:

Human Insulin (7.5 mg, 22.5 mg, 67.5 mg per day) is given orally daily together with food for the duration of the study.

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

Dosage and administration details:

Content of one capsule (7.5 mg, 22.5 mg or 67.5 mg Human insulin) is given orally daily together with food for the duration of the study.

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

Content of one capsule is given orally daily together with food for the duration of the study.

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

Dosage and administration details:

Placebo is given orally daily together with food for the duration of the study.

<b>Number of subjects in period 1</b>	Oral Insulin	Placebo
Started	22	22
Completed	21	20
Not completed	1	2
Adverse event, non-fatal	-	1
Dropped out due to illness of the sibling twin	1	-
due to social/familiar problems	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Oral Insulin
Reporting group description: Human Insulin (7.5 mg, 22.5 mg, 67.5 mg per day) is given orally daily together with food for the duration of the study.	
Reporting group title	Placebo
Reporting group description: Content of one capsule is given orally daily together with food for the duration of the study.	

Reporting group values	Oral Insulin	Placebo	Total
Number of subjects	22	22	44
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	20	18	38
Children (2-11 years)	2	4	6
Gender categorical Units: Subjects			
female	7	10	17
male	15	12	27

### Subject analysis sets

Subject analysis set title	INS AA genotype oral insulin
Subject analysis set type	Sub-group analysis
Subject analysis set description: Frequency of immune responses was compared between treatment groups in subjects with susceptible INS AA genotype.	
Subject analysis set title	INS AA genotype placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Frequency of immune responses was compared between treatment groups in subjects with susceptible INS AA genotype.	
Subject analysis set title	Safety / Insulin
Subject analysis set type	Safety analysis
Subject analysis set description: There was no difference between Placebo and Insulin group in: - blood glucose, - Insulin, - C-Peptide values, - the Insulin / C-Peptide ratio or - the areas under the concentration time curve for glucose, Insulin or C-Peptide.	
Subject analysis set title	Safety / Placebo
Subject analysis set type	Safety analysis
Subject analysis set description: There was no difference between Placebo and Insulin group in: - blood glucose, - Insulin, - C-Peptide values,	

- the Insulin / C-Peptide ratio or
- the areas under the concentration time curve for glucose, Insulin or C-Peptide.

Reporting group values	INS AA genotype oral insulin	INS AA genotype placebo	Safety / Insulin
Number of subjects	11	11	22
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	10	9	
Children (2-11 years)	1	2	
Gender categorical Units: Subjects			
female	2	6	
male	9	5	

Reporting group values	Safety / Placebo		
Number of subjects	21		
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Gender categorical Units: Subjects			
female			
male			

## End points

### End points reporting groups

Reporting group title	Oral Insulin
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Reporting group description:

Human Insulin (7.5 mg, 22.5 mg, 67.5 mg per day) is given orally daily together with food for the duration of the study.

Reporting group title	Placebo
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Reporting group description:

Content of one capsule is given orally daily together with food for the duration of the study.

Subject analysis set title	INS AA genotype oral insulin
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Frequency of immune responses was compared between treatment groups in subjects with susceptible INS AA genotype.

Subject analysis set title	INS AA genotype placebo
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Frequency of immune responses was compared between treatment groups in subjects with susceptible INS AA genotype.

Subject analysis set title	Safety / Insulin
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Subject analysis set type	Safety analysis
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Subject analysis set description:

There was no difference between Placebo and Insulin group in:

- blood glucose,
- Insulin,
- C-Peptide values,
- the Insulin / C-Peptide ratio or
- the areas under the concentration time curve for glucose, Insulin or C-Peptide.

Subject analysis set title	Safety / Placebo
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Subject analysis set type	Safety analysis
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Subject analysis set description:

There was no difference between Placebo and Insulin group in:

- blood glucose,
- Insulin,
- C-Peptide values,
- the Insulin / C-Peptide ratio or
- the areas under the concentration time curve for glucose, Insulin or C-Peptide.

### Primary: Immune response

End point title	Immune response
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End point description:

Immune response was defined as an increase in serum IgG antibodies to insulin, salivary IgA antibodies to insulin, or serum IAA and a CD4+ T cell response was defined as a stimulation index (SI) above 3 that was more than 2-fold increased over baseline.

End point type	Primary
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End point timeframe:

12 months (from baseline until end of treatment)

End point values	Oral Insulin	Placebo	INS AA genotype oral insulin	INS AA genotype placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	22	21	11	11
Units: subjects	12	14	9	7

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Oral Insulin
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.54 <sup>[1]</sup>
Method	Fisher exact

Notes:

[1] - The difference in the frequency of observed positive outcomes between the 2 treatment arms was not significant.

Statistical analysis title	Statistical Analysis 2
Comparison groups	INS AA genotype placebo v INS AA genotype oral insulin
Number of subjects included in analysis	22
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.64
Method	Fisher exact

## Secondary: Gene expression of insulin responsive CD4+ T-Cells at 12 months

End point title	Gene expression of insulin responsive CD4+ T-Cells at 12 months
End point description:	Gene expression values of insulin responsive CD4+ T-cells was measured as FOXP3 Treg/IFNg cell ratio
End point type	Secondary
End point timeframe:	at 12 months

End point values	Oral Insulin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	4		
Units: --				
median (inter-quartile range (Q1-Q3))	1.00 (1.00 to 1.00)	6.44 (4.61 to 14.00)		



## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Antibody Response to insulin

End point title	Antibody Response to insulin
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End point description:

End point type	Other pre-specified
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End point timeframe:

12 months (Baseline to End of treatment)

End point values	Oral Insulin	Placebo	INS AA genotype oral insulin	INS AA genotype placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	22	21	11	11
Units: subjects	9	7	8	2

## Statistical analyses

<b>Statistical analysis title</b>	Statistical Analysis 1
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Comparison groups	Oral Insulin v Placebo
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Number of subjects included in analysis	43
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.36
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Method	Fisher exact
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<b>Statistical analysis title</b>	Statistical Analysis 2
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Comparison groups	INS AA genotype oral insulin v INS AA genotype placebo
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Number of subjects included in analysis	22
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.03 <sup>[2]</sup>
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Method	Fisher exact
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Notes:

[2] - The difference in observed positive outcomes between the two treatment arms was significant.

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**Other pre-specified: CD4+ T-Cell Response to insulin**

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End point title	CD4+ T-Cell Response to insulin
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End point description:

End point type	Other pre-specified
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End point timeframe:

12 months ( Baseline until End of Treatment)

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End point values	Oral Insulin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	21		
Units: subjects	4	8		

**Statistical analyses**

Statistical analysis title	Statistical Analysis 1
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Comparison groups	Oral Insulin v Placebo
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Number of subjects included in analysis	43
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.19
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Method	Fisher exact
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**Other pre-specified: LOG2 CD4+ T-Cell Values at 9 months**

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End point title	LOG2 CD4+ T-Cell Values at 9 months
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End point description:

End point type	Other pre-specified
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End point timeframe:

at 9 months

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End point values	Oral Insulin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	21		
Units: SI (stimulation index)				
median (inter-quartile range (Q1-Q3))	0.54 (-0.09 to 0.99)	0.55 (0.20 to 0.93)		

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: LOG2 CD4+ T-Cell Values at 12 months

End point title	LOG2 CD4+ T-Cell Values at 12 months
End point description:	
End point type	Other pre-specified
End point timeframe:	
at 12 months	

End point values	Oral Insulin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	18		
Units: SI (stimulation index)				
median (inter-quartile range (Q1-Q3))	-0.04 (-0.47 to 0.21)	0.50 (-0.07 to 0.87)		

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: IGE Analysis Placebo versus Verum at 12 month

End point title	IGE Analysis Placebo versus Verum at 12 month
End point description:	
End point type	Other pre-specified
End point timeframe:	
At 12 month visit	

End point values	Safety / Insulin	Safety / Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	21		
Units: Subjects	17	17		

### Statistical analyses

Statistical analysis title	Analyse 1
Comparison groups	Safety / Insulin v Safety / Placebo
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.174
Method	Wilcoxon (Mann-Whitney)

### Other pre-specified: Safety

End point title	Safety
End point description:	
End point type	Other pre-specified
End point timeframe:	
Complete study duration	

End point values	Safety / Insulin	Safety / Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	21		
Units: Subjects	8	1		

### Statistical analyses

Statistical analysis title	Analysis 1 / Skin and subcutaneous tissue disorders
Comparison groups	Safety / Insulin v Safety / Placebo
Number of subjects included in analysis	43
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.011
Method	Logrank

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded throughout the study; documentation and assessment of AEs and SAEs occurred during 3 monthly visits.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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### Reporting groups

Reporting group title	Placebo
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Reporting group description:

Reference placebo, filled with microcrystalline cellulose as filling substance, orally, once daily for the duration of the study

Reporting group title	Verum
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Reporting group description:

Human Insulin (7.5mg, 22.5mg, 67.5mg), orally, once daily for the duration of the study

Serious adverse events	Placebo	Verum	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 21 (4.76%)	3 / 22 (13.64%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
burns second degree			
subjects affected / exposed	0 / 21 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stair fall			
subjects affected / exposed	0 / 21 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Invagination			
subjects affected / exposed	0 / 21 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Pneumonia right basal lobe subjects affected / exposed	1 / 21 (4.76%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive Pneumonia / Bronchitis subjects affected / exposed	1 / 21 (4.76%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis with dehydration subjects affected / exposed	0 / 21 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Placebo	Verum	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 21 (90.48%)	21 / 22 (95.45%)	
Investigations			
Temperature elevation			
subjects affected / exposed	1 / 21 (4.76%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
Burns second degree			
subjects affected / exposed	0 / 21 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Falling down			
subjects affected / exposed	0 / 21 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Fibula fracture			
subjects affected / exposed	0 / 21 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Wasp sting			
subjects affected / exposed	0 / 21 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	

Congenital, familial and genetic disorders Hydrozele subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 22 (4.55%) 1	
Surgical and medical procedures Inguinal hernia repair subjects affected / exposed occurrences (all)  Routine vaccination subjects affected / exposed occurrences (all)  Orchiopexy subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0  0 / 21 (0.00%) 0  1 / 21 (4.76%) 1	1 / 22 (4.55%) 1  1 / 22 (4.55%) 1  0 / 22 (0.00%) 0	
Blood and lymphatic system disorders Pancytopenia subjects affected / exposed occurrences (all)  Lymphadenitis subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0  0 / 21 (0.00%) 0	1 / 22 (4.55%) 1  1 / 22 (4.55%) 1	
General disorders and administration site conditions General malaise subjects affected / exposed occurrences (all)  Fever subjects affected / exposed occurrences (all)  Fatigue subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0  11 / 21 (52.38%) 18  0 / 21 (0.00%) 0	1 / 22 (4.55%) 3  14 / 22 (63.64%) 26  1 / 22 (4.55%) 1	
Immune system disorders Peanut allergy subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	0 / 22 (0.00%) 0	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	2 / 21 (9.52%)	8 / 22 (36.36%)	
occurrences (all)	2	10	
Invagination of intestine			
subjects affected / exposed	0 / 21 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Threw up			
subjects affected / exposed	0 / 21 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Stomatitis/Stomatitis aphthosa			
subjects affected / exposed	1 / 21 (4.76%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Teething/Teething pain			
subjects affected / exposed	2 / 21 (9.52%)	2 / 22 (9.09%)	
occurrences (all)	3	5	
Vomiting			
subjects affected / exposed	3 / 21 (14.29%)	4 / 22 (18.18%)	
occurrences (all)	3	6	
Tooth pain			
subjects affected / exposed	2 / 21 (9.52%)	2 / 22 (9.09%)	
occurrences (all)	3	6	
Respiratory, thoracic and mediastinal disorders			
Cough/Coughing			
subjects affected / exposed	4 / 21 (19.05%)	6 / 22 (27.27%)	
occurrences (all)	6	14	
Runny nose			
subjects affected / exposed	1 / 21 (4.76%)	5 / 22 (22.73%)	
occurrences (all)	1	5	
Sore throat			
subjects affected / exposed	0 / 21 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Reactive airways disease			
subjects affected / exposed	1 / 21 (4.76%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			



Diaper rash subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	2 / 22 (9.09%) 4	
Eczema subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 1	2 / 22 (9.09%) 2	
Erythema/Erythema facial subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 22 (4.55%) 2	
Exanthema subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 22 (4.55%) 1	
Pruritus subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 22 (4.55%) 1	
Urticaria subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 22 (4.55%) 2	
Infections and infestations Acute gastroenteritis/Gastroenteritis/Gastr oenteritis and fungal infection subjects affected / exposed occurrences (all)	7 / 21 (33.33%) 7	12 / 22 (54.55%) 20	
Bronchitis/Bronchitis viral subjects affected / exposed occurrences (all)	6 / 21 (28.57%) 7	6 / 22 (27.27%) 7	
Common cold subjects affected / exposed occurrences (all)	13 / 21 (61.90%) 25	10 / 22 (45.45%) 28	
Conjunctivitis subjects affected / exposed occurrences (all)	5 / 21 (23.81%) 5	5 / 22 (22.73%) 6	
Gingivitis subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 22 (4.55%) 1	
hand-mouth-feet disease			

subjects affected / exposed	3 / 21 (14.29%)	2 / 22 (9.09%)
occurrences (all)	3	2
croup		
subjects affected / exposed	1 / 21 (4.76%)	0 / 22 (0.00%)
occurrences (all)	1	0
Erysipelas		
subjects affected / exposed	1 / 21 (4.76%)	0 / 22 (0.00%)
occurrences (all)	2	0
Febrile cold (excl flu like illness)		
subjects affected / exposed	1 / 21 (4.76%)	2 / 22 (9.09%)
occurrences (all)	1	2
Impetigo		
subjects affected / exposed	1 / 21 (4.76%)	0 / 22 (0.00%)
occurrences (all)	1	0
Otitis / Otitis media		
subjects affected / exposed	4 / 21 (19.05%)	0 / 22 (0.00%)
occurrences (all)	5	0
Pneumonia/Obstructive pneumonia		
subjects affected / exposed	1 / 21 (4.76%)	0 / 22 (0.00%)
occurrences (all)	3	0
Respiratory tract infection bacterial		
subjects affected / exposed	1 / 21 (4.76%)	0 / 22 (0.00%)
occurrences (all)	1	0
Rhinitis		
subjects affected / exposed	4 / 21 (19.05%)	4 / 22 (18.18%)
occurrences (all)	11	4
Viral infection		
subjects affected / exposed	0 / 21 (0.00%)	2 / 22 (9.09%)
occurrences (all)	0	2
Oral infection		
subjects affected / exposed	0 / 21 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	1
Tonsillitis		
subjects affected / exposed	0 / 21 (0.00%)	2 / 22 (9.09%)
occurrences (all)	0	3
Herpes simplex		

subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0	1 / 22 (4.55%) 1	
Metabolism and nutrition disorders			
no appetite			
subjects affected / exposed	0 / 21 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
dehydration			
subjects affected / exposed	0 / 21 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 August 2015	<p>Investigator's Brochure (IB): Chapter 6 of the IB has been revised and updated. Furthermore, the results, especially the safety data, of the completed Pre-POINT study were described in more detail.</p> <p>Study protocol: (1) The benefit-risk analysis in chapter 2.6.1 and 2.6.2 was described in more detail with regard to the current results of the Pre-POINT study and other studies with oral insulin for the prevention of type 1 diabetes (DPT-1 study and TN07-TrialNet Oral Insulin Study) and analyzed with regard to the benefit-risk ratio on this basis. (2) The dosage information from international units has been added in Chapters 2.8 and 6.1.1. (3) It is also included in the study protocol that the study physician clearly indicates the risk of approximately 10% of patients suffering from type 1 diabetes during the consenting process (Chapter 7.2).</p> <p>Patient information and patient informed consent: The information on current study results was revised and presented in more detail.</p>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported