



## Clinical trial results:

### A 24-Week, Randomized, Open-Label, Parallel Group, Multicenter Comparison of Lantus® (Insulin Glargine) Given Once Daily Versus Neutral Protamine Hagedorn (NPH) Insulin in Children With Type 1 Diabetes Mellitus Aged At Least 6 Years to Less Than 18 Years

#### Summary

EudraCT number	2014-004640-35
Trial protocol	Outside EU/EEA
Global end of trial date	05 March 2014

#### Results information

Result version number	v1 (current)
This version publication date	01 April 2016
First version publication date	03 June 2015

#### Trial information

##### Trial identification

Sponsor protocol code	EFC11681
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01223131
WHO universal trial number (UTN)	U1111-1116-3661

Notes:

#### Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi Aventis Recherche & Developpement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi Aventis Recherche & Developpement, Contact-US@sanofi.com

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?	Yes

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 April 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	05 March 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To assess the efficacy of insulin glargine given once daily (QD) on glycosylated hemoglobin (HbA1c) levels over a period of 24 weeks in children with type 1 diabetes mellitus (T1DM) aged at least 6 years to less than 18 years.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of pediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia may have been used to minimize distress and discomfort.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 February 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	China: 162
Worldwide total number of subjects	162
EEA total number of subjects	0

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	65
Adolescents (12-17 years)	97
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 10 sites in China. A total of 196 subjects were screened between 11 February 2011 and 30 August 2013.

### Pre-assignment

Screening details:

Of 196 screened subjects, 31 were screen failures, 3 subjects were run-in failures and 162 subjects were randomized.

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

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

Arm description:

Insulin glargine for 24 weeks (+/- Rapid acting insulin)

Arm type	Experimental
Investigational medicinal product name	Insulin glargine
Investigational medicinal product code	HOE901
Other name	Lantus®
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin glargine 100 U/mL once daily at bedtime.

<b>Arm title</b>	NPH Insulin
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Arm description:

Neutral Protamine Hagedorn Insulin for 24 weeks ( +/- Rapid acting insulin)

Arm type	Active comparator
Investigational medicinal product name	NPH insulin
Investigational medicinal product code	
Other name	Novolin® N
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

NPH insulin 100 U/mL once daily (at bedtime) or twice daily (in the morning and at bedtime).

<b>Number of subjects in period 1</b>	Insulin Glargine	NPH Insulin
Started	107	55
Treated	107	54
Completed	106	50
Not completed	1	5
Adverse event	-	1
Poor compliance to protocol	1	4

## Baseline characteristics

### Reporting groups

Reporting group title	Insulin Glargine
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Reporting group description:

Insulin glargine for 24 weeks (+/- Rapid acting insulin)

Reporting group title	NPH Insulin
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Reporting group description:

Neutral Protamine Hagedorn Insulin for 24 weeks ( +/- Rapid acting insulin)

Reporting group values	Insulin Glargine	NPH Insulin	Total
Number of subjects	107	55	162
Age categorical			
Units: Subjects			
Children (2-11 years)	42	23	65
Adolescents (12-17 years)	65	32	97
Gender categorical			
Units: Subjects			
Female	63	36	99
Male	44	19	63
Body Mass Index (BMI)			
Number of subjects analysed for this outcome is 107 and 54 respectively.			
Units: kg per square meter			
arithmetic mean	18.7	18.2	
standard deviation	± 2.9	± 2.6	-
Duration of diabetes			
Number of subjects analysed for this outcome is 107 and 54 respectively.			
Units: years			
arithmetic mean	3.83	3.55	
standard deviation	± 2.93	± 2.25	-

## End points

### End points reporting groups

Reporting group title	Insulin Glargine
Reporting group description:	
Insulin glargine for 24 weeks (+/- Rapid acting insulin)	
Reporting group title	NPH Insulin
Reporting group description:	
Neutral Protamine Hagedorn Insulin for 24 weeks ( +/- Rapid acting insulin)	

### Primary: Absolute Change From Baseline in HbA1c at Week 24

End point title	Absolute Change From Baseline in HbA1c at Week 24 <sup>[1]</sup>
End point description:	
Analysis was carried out on modified intent-to-treat (mITT) population defined as all randomized and treated subjects, and had both a baseline assessment and at least one post-baseline assessment. Missing data imputed by Last Observation Carried Forward (LOCF).	
End point type	Primary
End point timeframe:	
From baseline to week 24	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive analysis was performed instead of hypothesis tests due to decrease of sample size during course of the study.

End point values	Insulin Glargine	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	51		
Units: percentage of haemoglobin				
arithmetic mean (standard deviation)	-0.25 (± 1.68)	-0.54 (± 1.67)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With HbA1c Value <7.5% at Week 24

End point title	Percentage of Subjects With HbA1c Value <7.5% at Week 24
End point description:	
Analysis was carried out on mITT population.	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	Insulin Glargine	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	51		
Units: percentage of subjects				
number (not applicable)	18.7	21.6		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Fasting Blood Glucose (FBG) at Week 24

End point title	Change From Baseline in Fasting Blood Glucose (FBG) at Week 24
End point description:	Analysis was carried out on mITT population. Missing data imputed by LOCF.
End point type	Secondary
End point timeframe:	From baseline to week 24

End point values	Insulin Glargine	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	52		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.76 (± 3.56)	1.07 (± 3.64)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Nocturnal Blood Glucose (BG) at Week 24

End point title	Change From Baseline in Nocturnal Blood Glucose (BG) at Week 24
End point description:	Nocturnal blood glucose was the value measured at 3:00 AM (clock time). Analysis was carried out on mITT population. Missing data imputed by LOCF.
End point type	Secondary
End point timeframe:	From baseline to week 24



End point values	Insulin Glargine	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	45		
Units: mmol/L				
arithmetic mean (standard deviation)	0.59 (± 6.16)	0.24 (± 5.8)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Average Blood Glucose Based on 8-Point Self-Monitoring Blood Glucose (SMBG)

End point title	Change From Baseline in Average Blood Glucose Based on 8-Point Self-Monitoring Blood Glucose (SMBG)
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End point description:

8-point SMBG was performed at 3:00 hours (clock time), before and 2 hours after each main meal (breakfast, lunch, and dinner), at bedtime (20-22 hours). Analysis was carried out on mITT population. Missing data imputed by LOCF.

End point type	Secondary
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End point timeframe:

From baseline to week 24

End point values	Insulin Glargine	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	53		
Units: mmol/L				
arithmetic mean (standard deviation)	0.01 (± 4.3)	-0.28 (± 3.92)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Total Insulin Dose And Basal Insulin Dose at Week 24

End point title	Change From Baseline in Total Insulin Dose And Basal Insulin Dose at Week 24
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End point description:

Analysis was carried out on mITT population. Missing data imputed by LOCF

End point type	Secondary
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End point timeframe:

From baseline to week 24

End point values	Insulin Glargine	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	53		
Units: units				
arithmetic mean (standard deviation)				
Total Insulin Dose	6.22 ( $\pm$ 7.54)	11.51 ( $\pm$ 12.06)		
Basal Insulin Dose	2.03 ( $\pm$ 3.36)	6.1 ( $\pm$ 7.09)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With Hypoglycemia

End point title	Percentage of Subjects With Hypoglycemia
End point description:	
Asymptomatic hypoglycemia: Blood glucose values <70 mg/dL (3.9 mmol/L) without clinical symptoms and/or signs. Symptomatic hypoglycemia: Any event with clinical symptoms that were considered to result from a hypoglycemic episode with an accompanying blood glucose <70 mg/dL (3.9 mmol/L). Severe symptomatic hypoglycemia: Any event with clinical symptoms considered to result from a hypoglycemic episode for which the subjects required the assistance of a third party (other than the subject or a parent/usual caregiver), with acute neurological impairment directly resulting from the hypoglycemic event. Nocturnal hypoglycemia: Any asymptomatic and/or symptomatic hypoglycemic event that occurred between 23:00 to 07:00 hours. Nocturnal symptomatic hypoglycemia: Any symptomatic hypoglycemic event that occurred between 23:00 to 07:00 hours. Analysis was carried out on safety population defined as all randomized and treated subjects and analyzed according to the treatment actually received.	
End point type	Secondary
End point timeframe:	
During 24-week treatment period	

End point values	Insulin Glargine	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	54		
Units: percentage of subjects				
number (not applicable)				
Subjects with any hypoglycemia	92.5	94.4		
Subjects with any symptomatic hypoglycemia	69.2	75.9		
Subjects with any asymptomatic hypoglycaemia	86.9	87		
Subjects with any severe symptomatic hypoglycaemia	0.9	1.9		
Subjects with any nocturnal hypoglycaemia	77.6	77.8		

Subjects with any nocturnal symptomatic hypoglycae	37.4	46.3		
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## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With Positive Anti-Insulin Glargine (AGA) Anti-Human Insulin (AIA) Antibody

End point title	Percentage of Subjects With Positive Anti-Insulin Glargine (AGA) Anti-Human Insulin (AIA) Antibody
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End point description:

Analysis was carried out on antibody population defined as all randomized subjects who contributed at least one evaluable blood sample at screening, or week 4, or week 24 (the end of treatment) for assessment of AGA and AIA.

End point type	Secondary
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End point timeframe:

At screening, week 4 and week 24

End point values	Insulin Glargine	NPH Insulin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	55		
Units: percentage of subjects				
number (not applicable)				
Positive AGA: Screening (n=107, 55)	69.2	78.2		
Positive AGA: Week 4 (n=107, 52)	68.2	73.1		
Positive AGA: Week 24 (n=106, 50)	65.1	78		
Positive AIA: Screening (n=107, 55)	60.7	69.1		
Positive AIA: Week 4 (n= 107, 52)	61.7	71.2		
Positive AIA: Week 24 (n=106, 50)	56.6	76		

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Week 24) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported adverse events are treatment-emergent adverse events that is AEs that developed/worsened during the 'on treatment period' (defined as the time from the first dose of study drug up to 7 days after the last dose of study drug administration).

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

### Reporting groups

Reporting group title	Insulin Glargine
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Reporting group description:

Insulin glargine for 24 weeks (+/- Rapid acting insulin).

Reporting group title	NPH Insulin
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Reporting group description:

Neutral Protamine Hagedorn Insulin for 24 weeks ( +/- Rapid acting insulin).

Serious adverse events	Insulin Glargine	NPH Insulin	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 107 (2.80%)	6 / 54 (11.11%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Blood Glucose Increased			
subjects affected / exposed	0 / 107 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis Acute			
subjects affected / exposed	1 / 107 (0.93%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Mumps			

subjects affected / exposed	1 / 107 (0.93%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	0 / 107 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic Ketoacidosis			
subjects affected / exposed	2 / 107 (1.87%)	3 / 54 (5.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 107 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Insulin Glargine	NPH Insulin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	81 / 107 (75.70%)	44 / 54 (81.48%)	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal Pain			
subjects affected / exposed	3 / 107 (2.80%)	3 / 54 (5.56%)	
occurrences (all)	6	3	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	28 / 107 (26.17%)	17 / 54 (31.48%)	
occurrences (all)	40	29	
Upper Respiratory Tract Infection			
subjects affected / exposed	18 / 107 (16.82%)	11 / 54 (20.37%)	
occurrences (all)	27	15	
Metabolism and nutrition disorders			

Hypoglycaemia subjects affected / exposed occurrences (all)	74 / 107 (69.16%) 1193	41 / 54 (75.93%) 789	
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## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 March 2013	<ul style="list-style-type: none"><li>- Change to the total sample size: The planned sample size was reduced from 366 to 150 subjects.</li><li>- The percentage with insulin glargine PK samples was increased from approximately 30% (about 73 subjects) to approximately 45% (about 45 subjects), in view of reduced sample size for Lantus population.</li><li>- In view of smaller sample size, descriptive statistical method was to be used instead of hypothesis tests (ANCOVA for continuous variables and Cochran-Mantel-Haenszel [CMH] for categorical variables) to show inferiority or superiority or estimating model (generalized linear model [GLM] for the event rate of hypoglycemia).</li><li>- Based upon the Investigator's clinical judgment, in cases where screening failure was only due to unqualified HbA1c value (HbA1c at screening &lt;7% or &gt;12%), the subject could be re-screened for this study after 6 months from last screening date. A subject could be randomized in this study only once.</li></ul>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported