Clinical trial results:
A randomised trial comparing efficacy and safety after intensification with either insulin aspart once daily as add-on or changing to basal bolus treatment with insulin degludec and insulin aspart in subjects with type 2 diabetes previously treated with insulin degludec/insulin aspart twice daily

Summary

EudraCT number	2012-003152-37
Trial protocol	DE
Global end of trial date	07 March 2014

Results information

Result version number	v1 (current)
This version publication date	15 March 2016
First version publication date	28 July 2015

Trial information

Trial identification

Sponsor protocol code	NN5401-4003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01814137
WHO universal trial number (UTN)	U1111-1132-2674

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Alle, Bagsvaerd, Denmark, 2880
Public contact	Global Clinical Registry (GCR,1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Global Clinical Registry (GCR,1452), Novo Nordisk A/S, clinicaltrials@novonordisk.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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 September 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 March 2014
Global end of trial reached?	Yes
Global end of trial date	07 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to compare efficacy of insulin degludec/insulin aspart (IDegAsp) twice daily (BID) + insulin aspart (IAsp) once daily (OD) vs. basal bolus with insulin degludec (IDeg) OD + IAsp three times a day (TID) in controlling glycaemia by evaluating glycosylated haemoglobin (HbA1c)

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2009), International Conference on Harmonisation Good Clinical Practice (1996), EN ISO 14155 Part 1 and 2, and FDA 21 CFR 312.120.

Background therapy:

DPP-4 inhibitor and/or metformin were the only allowed OAD treatments in trial NN5401-4003, and the dose and dosing frequency were not to be changed at any time during the 26-week treatment period, unless dose reductions were needed for safety reasons. Start of any new antidiabetic treatment was not allowed.

Evidence for comparator:

Not applicable

Actual start date of recruitment	12 March 2013
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	Germany: 2
Country: Number of subjects enrolled	Malaysia: 11
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	United States: 26
Worldwide total number of subjects	40
EEA total number of subjects	2

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	32
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 20 sites in 4 countries as follows: Germany: 1 site; Malaysia: 2 sites; Turkey: 1 site; United States: 16 sites. The subjects in this trial were to continue from trial NN5401-3941.

Pre-assignment

Screening details:

Subjects who did not reach the HbA1c target < 7.0% on IDegAsp BID after 26 weeks of treatment in trial NN5401-3941 were enrolled in this trial.

Period 1

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

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	IDegAsp BID + IAsp

Arm description:

Subjects randomised to IDegAsp BID + IAsp OD were, at the discretion of the investigator, to start the doses of IDegAsp taken with breakfast and main evening meal at Week 26 in trial NN5401-3941 and add 4 units of IAsp at lunch.

Arm type	Experimental
Investigational medicinal product name	IDegAsp
Investigational medicinal product code	
Other name	Insulin degludec/insulin aspart
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

IDegAsp was administered subcutaneously (s.c.) by injection in the thigh, the upper arm (deltoid area) or the abdominal wall and the chosen area of injection had to be the same throughout the trial. Rotation of injection sites within a given region was recommended. Titration (self-titration) of IDegAsp was performed once weekly.

Investigational medicinal product name	IAsp
Investigational medicinal product code	
Other name	Insulin aspart
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

IAsp was injected s.c. with the main meal OD, depending on the treatment arm, preferably into the abdominal wall in accordance with local labelling. Additional doses of IAsp were only allowed, if needed due to intercurrent illness. Titration (self-titration) of IAsp was performed once weekly. Titration of IAsp could also be done based on carbohydrate counting but at the investigator's discretion. Dose reduction had to be done based on the investigator's discretion.

Arm title	IDeg OD + IAsp

Arm description:

Subjects randomised to IDeg OD + IAsp TID were, at the discretion of the investigator, to start with 70% of the total daily dose of IDegAsp taken at Week 26 in trial NN5401-3941 as IDeg OD and 30% as IAsp divided into three doses.

Arm type	Active comparator
Investigational medicinal product name	IDeg
Investigational medicinal product code	
Other name	Insulin degludec
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

IDeg was administered s.c. by injection in the thigh, the upper arm (deltoid area) or the abdominal wall and the chosen area of injection had to be the same throughout the trial. Rotation of injection sites within a given region was recommended. When needed, the subjects had the option of changing the OD injection time from day to day. Titration (self-titration) of IDeg was performed once weekly.

Investigational medicinal product name	IAsp
Investigational medicinal product code	
Other name	Insulin aspart
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

IAsp was injected s.c. with the main meals TID, depending on the treatment arm, preferably into the abdominal wall in accordance with local labelling. Additional doses of IAsp were only allowed, if needed due to intercurrent illness. Titration (self-titration) of IAsp was performed once weekly. Titration of IAsp could also be done based on carbohydrate counting but at the investigator's discretion. Dose reduction had to be done based on the investigator's discretion.

Number of subjects in period 1	IDegAsp BID + IAsp	IDeg OD + IAsp
Started	20	20
Completed	15	15
Not completed	5	5
Adverse event, non-fatal	-	1
Withdrawal criteria	3	3
Unclassified	2	1

Baseline characteristics

Reporting groups	
Reporting group title	IDegAsp BID + IAsp
Reporting group description:	
Subjects randomised to IDegAsp BID + IAsp OD were, at the discretion of the investigator, to start the doses of IDegAsp taken with breakfast and main evening meal at Week 26 in trial NN5401-3941 and add 4 units of IAsp at lunch.	
Reporting group title	IDeg OD + IAsp
Reporting group description:	
Subjects randomised to IDeg OD + IAsp TID were, at the discretion of the investigator, to start with 70% of the total daily dose of IDegAsp taken at Week 26 in trial NN5401-3941 as IDeg OD and 30% as IAsp divided into three doses.	

Reporting group values	IDegAsp BID + IAsp	IDeg OD + IAsp	Total
Number of subjects	20	20	40
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)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	16	16	32
From 65-84 years	4	4	8
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	58	56.9	
standard deviation	± 8	± 8.1	-
Gender categorical			
Units: Subjects			
Female	5	9	14
Male	15	11	26
Body weight			
Units: Kg			
arithmetic mean	90.4	85.3	
standard deviation	± 20.7	± 20.2	-
Body Mass Index			
Units: kg/m2			
arithmetic mean	31.7	31.1	
standard deviation	± 5.3	± 6.2	-
Glycosylated haemoglobin (HbA1c)			
Units: Percentage (%)			
arithmetic mean	7.9	7.7	
standard deviation	± 0.7	± 0.6	-
Fasting plasma glucose (FPG)			
Units: mmol/L			

arithmetic mean	7.3	8.6	
standard deviation	± 3.5	± 2.8	-

End points

End points reporting groups

Reporting group title	IDegAsp BID + IAsp
Reporting group description:	
Subjects randomised to IDegAsp BID + IAsp OD were, at the discretion of the investigator, to start the doses of IDegAsp taken with breakfast and main evening meal at Week 26 in trial NN5401-3941 and add 4 units of IAsp at lunch.	
Reporting group title	IDeg OD + IAsp
Reporting group description:	
Subjects randomised to IDeg OD + IAsp TID were, at the discretion of the investigator, to start with 70% of the total daily dose of IDegAsp taken at Week 26 in trial NN5401-3941 as IDeg OD and 30% as IAsp divided into three doses.	

Primary: Change from baseline in HbA1c (%)

End point title	Change from baseline in HbA1c (%)
End point description:	
Percentage point change in glycosylated haemoglobin A1c (HbA1c) during 26 weeks of treatment.	
End point type	Primary
End point timeframe:	
Mean change from baseline in HbA1c during 26 weeks of treatment.	

End point values	IDegAsp BID + IAsp	IDeg OD + IAsp		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Percentage (%)				
least squares mean (standard error)	0.05 (± 0.2)	-0.49 (± 0.19)		

Statistical analyses

Statistical analysis title	HbA1c (%) after 26 weeks of treatment
Statistical analysis description:	
Change from baseline in HbA1c after 26 weeks of treatment was to be analysed using an Analysis of Variance (ANOVA) method with treatment, sex and region as fixed factors, and age and baseline HbA1c as covariates. The region was a factor with four levels: 1. North America, 2. Europe, 3. Asia, and 4. Africa.	
Comparison groups	IDegAsp BID + IAsp v IDeg OD + IAsp
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.021 [2]
Method	ANOVA
Parameter estimate	Mean difference (Change from Baseline)
Point estimate	0.54

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.99
Variability estimate	Standard error of the mean

Notes:

[1] - It is a comparison trial.

[2] - P-values were only to be presented for the primary endpoint. The other endpoints were considered supportive and explorative in nature and, hence, no p-values were to be presented.

Secondary: Incidence of treatment emergent adverse events (TEAEs)

End point title	Incidence of treatment emergent adverse events (TEAEs)

End point description:

A treatment emergent adverse event was defined as an event that had onset date on or after the first day of trial product
administration, and no later than 7 days after the last dose of the trial product.

End point type	Secondary

End point timeframe:

During 26 weeks of treatment.

End point values	IDegAsp BID + IAsp	IDeg OD + IAsp		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: number of events	33	45		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment emergent hypoglycaemic episodes both according to Novo Nordisk definition of confirmed hypoglycaemic episodes (severe hypoglycaemia and /or a measured plasma glucose (PG)< 3.1 mmol/L (56 mg/dL) as well as to the ADA definition.

End point title	Number of treatment emergent hypoglycaemic episodes both according to Novo Nordisk definition of confirmed hypoglycaemic episodes (severe hypoglycaemia and /or a measured plasma glucose (PG)< 3.1 mmol/L (56 mg/dL) as well as to the ADA definition.

End point description:

Confirmed hypoglycaemic episodes were defined as episodes that are either:
- severe (i.e., an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions) or
- biochemically confirmed by a PG value of <3.1 mmol/L (56 mg/dL), with or without symptoms consistent with hypoglycaemia.

End point type	Secondary

End point timeframe:

During 26 weeks of treatment.

End point values	IDegAsp BID + IAsp	IDeg OD + IAsp		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Number of events	54	95		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment emergent nocturnal (00:01-05:59 am) confirmed hypoglycaemic episodes.

End point title	Number of treatment emergent nocturnal (00:01-05:59 am) confirmed hypoglycaemic episodes.

End point description:

Hypoglycaemic episodes were defined as nocturnal if the time of onset was between 00:01 and 05:59 hours inclusive.

End point type	Secondary

End point timeframe:

During 26 weeks of treatment.

End point values	IDegAsp BID + IAsp	IDeg OD + IAsp		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: number of confirmed events	13	12		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in fasting plasma glucose (FPG)

End point title	Change from baseline in fasting plasma glucose (FPG)

End point description:

FPG was analysed on blood samples from fasting subjects which were analysed centrally.

End point type	Secondary

End point timeframe:

After 26 weeks of treatment.

End point values	IDegAsp BID + IAsp	IDeg OD + IAsp		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: mmol/L				
arithmetic mean (standard deviation)	-0.8 (± 3.59)	-2.57 (± 2.73)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were captured on the onset date on or after the first day of exposure to randomised treatment and no later than the last day of randomised treatment.

Adverse event reporting additional description:

Safety analysis set included all subjects receiving at least one dose of the investigational product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	IDegAsp BID + IAsp

Reporting group description:

Subjects randomised to IDegAsp BID + IAsp OD were, at the discretion of the investigator, to start the doses of IDegAsp taken with breakfast and main evening meal at Week 26 in trial NN5401-3941 and add 4 units of IAsp at lunch.

Reporting group title	IDeg OD + IAsp

Reporting group description:

Subjects randomised to IDeg OD + IAsp TID were, at the discretion of the investigator, to start with 70% of the total daily dose of IDegAsp taken at Week 26 in trial NN5401-3941 as IDeg OD and 30% as IAsp divided into three doses.

Serious adverse events	IDegAsp BID + IAsp	IDeg OD + IAsp	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 20 (10.00%)	2 / 20 (10.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			

subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Peptic ulcer haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	IDegAsp BID + IAsp	IDeg OD + IAsp	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 20 (75.00%)	16 / 20 (80.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fibroadenoma of breast			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Oedema peripheral			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Pyrexia			
subjects affected / exposed	1 / 20 (5.00%)	4 / 20 (20.00%)	
occurrences (all)	1	6	
Immune system disorders			

Food allergy			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Cough			
subjects affected / exposed	1 / 20 (5.00%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Dyspnoea			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Muscle strain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Tendon rupture			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Thermal burn			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Wrong drug administered			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			

Lymphadenopathy			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Diabetic retinopathy			
subjects affected / exposed	3 / 20 (15.00%)	0 / 20 (0.00%)	
occurrences (all)	3	0	
Eye swelling			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Macular oedema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Retinal aneurysm			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 20 (5.00%)	2 / 20 (10.00%)	
occurrences (all)	2	3	
Diarrhoea			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	2	
Lip swelling			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	

Hidradenitis			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Pruritus			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Back pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Rheumatoid arthritis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Acute sinusitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Dengue fever			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Eye infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	

Hordeolum			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Otitis media			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Subcutaneous abscess			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Tinea pedis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 20 (5.00%)	5 / 20 (25.00%)	
occurrences (all)	1	5	
Urinary tract infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the highly selected trial population randomised in this trial (N=40), the results should be interpreted with caution.

Notes: