

**Clinical trial results:**

A randomised controlled trial comparing the effect of the faster-acting insulin analog - insulin Fiasp® – versus insulin Novorapid® in the treatment of women with type 1 or type 2 diabetes during pregnancy and lactation

Summary

EudraCT number	2018-004680-31
Trial protocol	DK
Global end of trial date	23 March 2023

Results information

Result version number	v1 (current)
This version publication date	30 October 2023
First version publication date	30 October 2023
Summary attachment (see zip file)	Published study results Lancet Diabetes Endocrinology (Copenfast artikel Lancet Diab Endocrinol 2023.pdf)

Trial information**Trial identification**

Sponsor protocol code	2018-004680-31
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03770767
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rigshospitalet University Hospital of Copenhagen
Sponsor organisation address	Blegdamsvej 9, Copenhagen, Denmark, 2100
Public contact	Principal investigator, Lene Ringholm, 45 35451336, lene.ringholm.02@regionh.dk
Scientific contact	Principal investigator, Lene Ringholm, 45 35451336, lene.ringholm.02@regionh.dk

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	25 April 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 March 2023
Global end of trial reached?	Yes
Global end of trial date	23 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective is to evaluate the effect of insulin Fiasp® compared to insulin NovoRapid®, both in combination with usual long-acting insulin when indicated, on postprandial glucose levels, HbA1c, prevalence of fetal overgrowth in women with type 1 or type 2 diabetes during pregnancy. Infant growth and health up to 3 months of age will also be evaluated.

The incidence of mild and severe hypoglycemia and the potential of blinded CGM to predict fetal overgrowth will be evaluated. The most appropriate insulin pump settings during pregnancy and lactation will be explored.

Protection of trial subjects:

The trial protocol was approved by The Danish Medicines Agency (2018-004680-31) and the Regional Ethics Committee (H-19029966), and was published before completed enrollment. The trial was conducted in accordance with the Good Clinical Practice guidelines and monitored by the local GCP unit. Written informed consent was obtained by all participants prior to trial participation and by the participants' partners regarding data collection of the infant prior to delivery.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 November 2019
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	Denmark: 216
Worldwide total number of subjects	216
EEA total number of subjects	216

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)	216
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first contact with the women with type 1 or type 2 diabetes referred to our center took place in early pregnancy at the first antenatal visit at our center. The women with type 1 or type 2 diabetes were contacted by a diabetes caregiver and invited orally and in writing to participate in this trial. The women had time to consider participation.

Pre-assignment

Screening details:

Eligibility assessment with regards to inclusion and exclusion criteria was performed. If any inclusion criterion was answered "no" or any exclusion criterion answered "yes" the woman was a screening failure and no further assessment was done. Re-screening was not allowed if the woman had failed one of the inclusion or exclusion criteria.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention

Arm description:

Women randomized to intervention with faster-acting insulin aspart

Arm type	Experimental
Investigational medicinal product name	Faster aspart
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Faster aspart (100 U/mL) was continued from before pregnancy in those using insulin before pregnancy. For participants initiating insulin at randomization, 0.3 U/kg body weight was given. The dose of faster aspart was titrated based on blood glucose monitoring. During pregnancy all participants were encouraged to adjust mealtime insulin dose every 3-5 days between the routine visits, when appropriate, to obtain BGM targets 4-5.5 mmol/L pre-prandially, 4-7 mmol/L postprandially and 5-7 mmol/L before bedtime. Post-delivery the BGM targets were 4.0-7.0 mmol/L pre-prandially and 6.0-10.0 mmol/L before bedtime.

Arm title	Control
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Arm description:

Women randomized to active comparator insulin aspart

Arm type	Active comparator
Investigational medicinal product name	Aspart
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin aspart (100 U/mL) was continued from before pregnancy in those using insulin before pregnancy. For participants initiating insulin at randomization 0.3 U/kg body weight was given. The insulin aspart dose was titrated based on blood glucose monitoring. During pregnancy all participants were encouraged to adjust mealtime insulin dose every 3-5 days between the routine visits, when appropriate, to obtain BGM targets 4-5.5 mmol/L pre-prandially, 4-7 mmol/L postprandially and 5-7

mmol/L before bedtime. Post-delivery the BGM targets were 4.0-7.0 mmol/L pre-prandially and 6.0-10.0 mmol/L before bedtime.

Number of subjects in period 1	Intervention	Control
Started	109	107
Completed	101	102
Not completed	8	5
Consent withdrawn by subject	1	-
Lost to follow-up	7	5

Baseline characteristics

Reporting groups

Reporting group title	Intervention
Reporting group description: Women randomized to intervention with faster-acting insulin aspart	
Reporting group title	Control
Reporting group description: Women randomized to active comparator insulin aspart	

Reporting group values	Intervention	Control	Total
Number of subjects	109	107	216
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)	109	107	216
From 65-84 years	0	0	0
85 years and over	0	0	0
18-64	0	0	0
Age continuous			
Units: years			
arithmetic mean	31.7	31.6	
standard deviation	± 5.1	± 5.3	-
Gender categorical			
Pregnant women			
Units: Subjects			
Female	109	107	216
Male	0	0	0

Subject analysis sets

Subject analysis set title	Intervention
Subject analysis set type	Intention-to-treat
Subject analysis set description: The primary data analyses included all randomised participants according to the intention-to-treat principle.	
Subject analysis set title	Control
Subject analysis set type	Intention-to-treat
Subject analysis set description: The primary data analyses included all randomised participants according to the intention-to-treat principle.	

Reporting group values	Intervention	Control	
Number of subjects	101	102	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	101	102	
From 65-84 years	0	0	
85 years and over	0	0	
18-64	0	0	
Age continuous			
Units: years			
arithmetic mean	31.6	31.8	
standard deviation	± 5.2	± 5.3	
Gender categorical			
Pregnant women			
Units: Subjects			
Female	101	102	
Male	0	0	

End points

End points reporting groups

Reporting group title	Intervention
Reporting group description: Women randomized to intervention with faster-acting insulin aspart	
Reporting group title	Control
Reporting group description: Women randomized to active comparator insulin aspart	
Subject analysis set title	Intervention
Subject analysis set type	Intention-to-treat
Subject analysis set description: The primary data analyses included all randomised participants according to the intention-to-treat principle.	
Subject analysis set title	Control
Subject analysis set type	Intention-to-treat
Subject analysis set description: The primary data analyses included all randomised participants according to the intention-to-treat principle.	

Primary: Offspring birthweight standard deviation score

End point title	Offspring birthweight standard deviation score
End point description:	
End point type	Primary
End point timeframe: Participants were randomized between November 11 2019 and May 10 2022. Primary end point was collected when participants delivered mean 37 weeks after randomization.	

End point values	Intervention	Control	Intervention	Control
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	101	102	101	102
Units: gram(s)				
arithmetic mean (standard deviation)	1.0 (\pm 1.4)	1.2 (\pm 1.3)	1.0 (\pm 1.4)	1.2 (\pm 1.3)

Statistical analyses

Statistical analysis title	Statistical analysis
Statistical analysis description: The primary outcome was analyzed by multiple linear regression adjusted for the stratification variable.	
Comparison groups	Intervention v Control

Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.5
Method	Regression, Linear

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From November 11 2019 to March 23 2023.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22
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Reporting groups

Reporting group title	Intervention
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Reporting group description: -

Reporting group title	Comparator
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Reporting group description: -

Serious adverse events	Intervention	Comparator	
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 109 (30.28%)	25 / 107 (23.36%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Congenital, familial and genetic disorders			
Congenital malformations			
subjects affected / exposed	8 / 109 (7.34%)	6 / 107 (5.61%)	
occurrences causally related to treatment / all	0 / 8	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
pregnancy			
subjects affected / exposed	25 / 109 (22.94%)	19 / 107 (17.76%)	
occurrences causally related to treatment / all	0 / 25	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Intervention	Comparator	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 109 (75.23%)	85 / 107 (79.44%)	

Reproductive system and breast disorders			
Pregnancy			
subjects affected / exposed	82 / 109 (75.23%)	85 / 107 (79.44%)	
occurrences (all)	82	85	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 March 2020	From March 12 to May 1 2020: Inclusion paused due to COVID-19 pandemic.
01 September 2020	Participants were planned to be offered blinded continuous glucose monitoring (CGM, Envision Pro Sensor, Medtronic MiniMed) for seven days following randomisation, at 21 and 33 weeks, and in the morning for planned induction of labour or caesarean section. However, this blinded CGM was withdrawn from the market during the trial. Participants using continuous glucose monitoring (CGM) routinely continued their use regardless type of CGM device. The remaining participants with type 1 diabetes were offered intermittently scanned CGM from early pregnancy as part of routine care
27 April 2021	The pre-planned inclusion period of two years was extended by six months to meet the prespecified sample size.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/37804858>