

**Clinical trial results:****A trial investigating ultra-long-acting basal insulins' flexibility around multiple spontaneous exercise sessions in people with type 1 diabetes: a head to head comparison of 2nd generation insulin Glargine U300 (IGlar-U300) to insulin Degludec U100 (IDeg-U100)****Summary**

EudraCT number	2019-003209-89
Trial protocol	AT
Global end of trial date	13 December 2021

Results information

Result version number	v1 (current)
This version publication date	19 July 2023
First version publication date	19 July 2023

Trial information**Trial identification**

Sponsor protocol code	ULTRAFLEXI1
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	DRKS: DRKS00018065

Notes:

Sponsors

Sponsor organisation name	Medical University of Graz
Sponsor organisation address	Neue Stiftingtalstrasse 6, Graz, Austria,
Public contact	Mag. Alexander Müller (Project Management), Medical University of Graz, alexander.mueller@medunigraz.at
Scientific contact	Prof. Dr. Harald Sourij (Principal Investigator), Medical University of Graz, ha.sourij@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:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 March 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 December 2021
Global end of trial reached?	Yes
Global end of trial date	13 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective

To compare time spent in hypoglycaemia (< 3.9 mmol/L [$<70\text{mg/dL}$]) for the 6 x 24-hour post-exercise period around multiple spontaneous exercise sessions (3 times per week spread over 2 weeks for each trial arm) on either a regular (100%) or 75% IGlax-U300 and IDeg-U100 dose

Protection of trial subjects:

Adverse events, hypoglycaemic episodes (also defined as a safety outcome), laboratory safety variables (hematology, biochemistry, coagulation, urinalysis), physical examination, vital signs, and electrocardiogram will be recorded during the study period.

pre-, during- and post-exercise sessions blood glucose will be measured and carbohydrates will be given if necessary

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 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	Austria: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

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)	25
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects will be recruited from the participant database kept at the trial site

Pre-assignment

Screening details:

Screening Visit: oral and written infos. After signing IC at the screening Visit participants will be screened for eligibility. They perform a cardiopulmonary exercise test to determine the peak oxygen uptake. They get applicated a blinded CGM device. Based on randomization of the type of insulin they will be titrated. Discussion of all procedures.

Period 1

Period 1 title	Time spent in hypoglycaemia Ideg 100%
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	IDeg-U100 100% regular dose
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Arm description:

Out of a total of 24 training units, 25 participants performed 6 constant load exercise sessions with the regular 100% dosage of the insulin IDeg-U100.

Arm type	Active comparator
Investigational medicinal product name	IDeg-U100
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants receive a phone call from the research team at 08.00 that contains the information to inject at 10.00 a regular basal insulin dose of randomized insulin and dosage. The exercise sessions will be performed at 18:00 at the trial unit center. Based on the randomization of the type of basal insulin, participants will be titrated to IGlax-U300 or IDeg-U100 over a maximum titration period of 4 weeks to achieve a morning fasted blood glucose concentration of 80 - 130 mg/dL (4.4 - 7.2 mmol/L) over 3 consecutive days. For both basal insulins, the first dose is 0.3 IU/kg body weight. Participants will administer IGlax-U300 and IDeg-U100 as a subcutaneous injection into a lifted skin fold on the surface of the abdomen or thigh.

Number of subjects in period 1	IDeg-U100 100% regular dose
Started	25
Completed	25

Period 2

Period 2 title	Time spent in hypoglycaemia Ideg 75%
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	IDeg-U100 75% reduced dose
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Arm description:

Out of a total of 24 training units, 25 participants performed 6 constant load exercise sessions with the reduced 75% dosage of the insulin IDeg-U100.

Arm type	Experimental
Investigational medicinal product name	IDeg-U100
Investigational medicinal product code	
Other name	Tresiba
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants receive a phone call from the research team at 08.00 that contains the information to inject at 10.00 a reduced basal insulin dose of randomized insulin and dosage. The exercise sessions will be performed at 18:00 at the trial unit center. Based on the randomization of the type of basal insulin, participants will be titrated to IGlax-U300 or IDeg-U100 over a maximum titration period of 4 weeks to achieve a morning fasted blood glucose concentration of 80 - 130 mg/dL (4.4 - 7.2 mmol/L) over 3 consecutive days. For both basal insulins, the first dose is 0.3 IU/kg body weight. Participants will administer IGlax-U300 and IDeg-U100 as a subcutaneous injection into a lifted skin fold on the surface of the abdomen or thigh.

Number of subjects in period 2	IDeg-U100 75% reduced dose
Started	25
Completed	25

Period 3

Period 3 title	Time spent in hypoglycaemia Iglar 100%
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	IGlar-U300 100% regular dose
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Arm description:

Out of a total of 24 training units, 25 participants performed 6 constant load exercise sessions with the regular 100% dosage of the insulin IGlax-U300.

Arm type	Experimental
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Investigational medicinal product name	IGlar-U300
Investigational medicinal product code	
Other name	Toujeo
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants receive a phone call from the research team at 08.00 that contains the information to inject at 10.00 a regular basal insulin dose of randomized insulin and dosage. The exercise sessions will be performed at 18:00 at the trial unit center. Based on the randomization of the type of basal insulin, participants will be titrated to IGLar-U300 or IDeg-U100 over a maximum titration period of 4 weeks to achieve a morning fasted blood glucose concentration of 80 - 130 mg/dL (4.4 - 7.2 mmol/L) over 3 consecutive days. For both basal insulins, the first dose is 0.3 IU/kg body weight. Participants will administer IGLar-U300 and IDeg-U100 as a subcutaneous injection into a lifted skin fold on the surface of the abdomen or thigh.

Number of subjects in period 3	IGlar-U300 100% regular dose
Started	25
Completed	25

Period 4

Period 4 title	Time spent in hypoglycaemia Iglar 75%
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	IGlar-U300 75% reduced dose
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Arm description:

Out of a total of 24 training units, 25 participants performed 6 constant load exercise sessions with the reduced 75% dosage of the insulin IGLar-U300.

Arm type	Experimental
Investigational medicinal product name	IGlar-U300
Investigational medicinal product code	
Other name	Toujeo
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants receive a phone call from the research team at 08.00 that contains the information to inject at 10.00 a reduced basal insulin dose of randomized insulin and dosage. The exercise sessions will be performed at 18:00 at the trial unit center. Based on the randomization of the type of basal insulin, participants will be titrated to IGLar-U300 or IDeg-U100 over a maximum titration period of 4 weeks to achieve a morning fasted blood glucose concentration of 80 - 130 mg/dL (4.4 - 7.2 mmol/L) over 3 consecutive days. For both basal insulins, the first dose is 0.3 IU/kg body weight. Participants will administer IGLar-U300 and IDeg-U100 as a subcutaneous injection into a lifted skin fold on the surface of the abdomen or thigh.

Number of subjects in period 4	IGlar-U300 75% reduced dose
Started	25
Completed	25

Baseline characteristics

Reporting groups

Reporting group title	Time spent in hypoglycaemia Ideg 100%
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Reporting group description: -

Reporting group values	Time spent in hypoglycaemia Ideg 100%	Total	
Number of subjects	25	25	
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)	25	25	
From 65-84 years	0	0	
85 years and over	0	0	
Adults (18-65)	0	0	
Age continuous Units: years			
arithmetic mean	41.4		
standard deviation	± 11.9	-	
Gender categorical Units: Subjects			
Female	11	11	
Male	14	14	

End points

End points reporting groups

Reporting group title	IDeg-U100 100% regular dose
Reporting group description: Out of a total of 24 training units, 25 participants performed 6 constant load exercise sessions with the regular 100% dosage of the insulin IDeg-U100.	
Reporting group title	IDeg-U100 75% reduced dose
Reporting group description: Out of a total of 24 training units, 25 participants performed 6 constant load exercise sessions with the reduced 75% dosage of the insulin IDeg-U100.	
Reporting group title	IGlar-U300 100% regular dose
Reporting group description: Out of a total of 24 training units, 25 participants performed 6 constant load exercise sessions with the regular 100% dosage of the insulin IGlar-U300.	
Reporting group title	IGlar-U300 75% reduced dose
Reporting group description: Out of a total of 24 training units, 25 participants performed 6 constant load exercise sessions with the reduced 75% dosage of the insulin IGlar-U300.	

Primary: Time below range <70mg/dL during 24h post exercise periods of six spontaneous exercise sessions in the four trial arms on either a regular (100%) or reduced (75%) IGlar-U300 and Ideg-U100 dose

End point title	Time below range <70mg/dL during 24h post exercise periods of six spontaneous exercise sessions in the four trial arms on either a regular (100%) or reduced (75%) IGlar-U300 and Ideg-U100 dose
End point description:	
End point type	Primary
End point timeframe: Data collection over a period of 19 months.	

End point values	IDeg-U100 100% regular dose	IDeg-U100 75% reduced dose	IGlar-U300 100% regular dose	IGlar-U300 75% reduced dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	25	25	25
Units: CGM Data, Blood Glucose				
arithmetic mean (standard deviation)	4.37 (± 0.69)	2.55 (± 0.58)	2.71 (± 0.51)	2.28 (± 0.53)

Statistical analyses

Statistical analysis title	Comparison of IGlar-U300 with Ideg-U100
Comparison groups	IDeg-U100 100% regular dose v IDeg-U100 75% reduced dose v IGlar-U300 100% regular dose v IGlar-U300 75% reduced dose

Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.05
Method	Mixed models analysis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

11.05.2020 - 13.12.2021

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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Reporting groups

Reporting group title	insert a cannula in the antecubital vein
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Reporting group description:

The subject reports dizziness and discomfort during the placement of a venous access.

Reporting group title	cold/elevated temperature/cough
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Reporting group description: -

Reporting group title	headaches/migraine
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Reporting group description: -

Reporting group title	vaccination reaction (COVID)
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Reporting group description:

tiredness, headache, elevated temperature, prick pain

Reporting group title	bicycle accident
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Reporting group description:

While dismounting from the bicycle, the subject hit their head and had to be treated. (Leisure accident)

Reporting group title	nausea and dizziness after max. CPX text
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Reporting group description:

The subject felt nausea and dizziness at the end/ after a maximum cardiopulmonary exercise test (CPX).

Reporting group title	Hyperglycemia before visit
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Reporting group description:

The subject is in hyperglycemic conditions before the start of the visit.

Serious adverse events	insert a cannula in the antecubital vein	cold/elevated temperature/cough	headaches/migraine
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	vaccination reaction (COVID)	bicycle accident	nausea and dizziness after max. CPX text
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 1 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Hyperglycemia before visit		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 2.5 %

Non-serious adverse events	insert a cannula in the antecubital vein	cold/elevated temperature/cough	headaches/migraine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	5 / 5 (100.00%)	2 / 2 (100.00%)
Investigations			
insert a cannula in the antecubital vein			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 1 (100.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
vaccination reaction (COVID)			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
nausea and dizziness after max. CPX test			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
bicycle accident			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
cold/elevated temperature/cough			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 1 (0.00%)	5 / 5 (100.00%)	0 / 2 (0.00%)
occurrences (all)	0	5	0
headaches/migraine			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1 (0.00%)	0 / 5 (0.00%)	2 / 2 (100.00%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Hyperglycemia before visit			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 1 (0.00%)	0 / 5 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	vaccination reaction (COVID)	bicycle accident	nausea and dizziness after max. CPX text
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	1 / 1 (100.00%)	1 / 1 (100.00%)
Investigations			
insert a cannula in the antecubital vein			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
vaccination reaction (COVID)			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 4 (100.00%)	0 / 1 (0.00%)	0 / 1 (0.00%)
occurrences (all)	4	0	0
nausea and dizziness after max. CPX text			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	1 / 1 (100.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
bicycle accident			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 4 (0.00%)	1 / 1 (100.00%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			

cold/elevated temperature/cough alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0
headaches/migraine alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0
Metabolism and nutrition disorders Hyperglycemia before visit alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0

Non-serious adverse events	Hyperglycemia before visit		
Total subjects affected by non-serious adverse events subjects affected / exposed	1 / 1 (100.00%)		
Investigations insert a cannula in the antecubital vein alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
vaccination reaction (COVID) alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
nausea and dizziness after max. CPX test alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Injury, poisoning and procedural complications bicycle accident alternative assessment type: Non-systematic			

subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Infections and infestations cold/elevated temperature/cough alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) headaches/migraine alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
Metabolism and nutrition disorders Hyperglycemia before visit alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1		

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

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/36516429>