Clinical trial results:
Insulin Therapy for the Prevention of New Onset Diabetes after Transplantation (ITP-NODAT) Prospective Study in Non-Diabetic De Novo Kidney Transplant Recipients

Summary

EudraCT number	2012-000225-51
Trial protocol	ES AT
Global end of trial date	06 August 2018

Results information

Result version number	v1 (current)
This version publication date	03 October 2020
First version publication date	03 October 2020

Trial information

Trial identification

Sponsor protocol code	ITP-NODAT

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Medical University of Vienna
Sponsor organisation address	Währinger Gürtel 18-20, Vienna, Austria, 1090
Public contact	Manfred Hecking , Klinische Abteilung für Nephrologie und Dialyse, 0043 4040043901, manfred.hecking@meduniwien.ac.at
Scientific contact	Manfred Hecking, Klinische Abteilung für Nephrologie und Dialyse, 0043 4040043901, manfred.hecking@meduniwien.ac.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	23 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 May 2018
Global end of trial reached?	Yes
Global end of trial date	06 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study aims to assess the effects of early insulin therapy in previously non-diabetic de novo kidney transplant patients in reducing the incidence of new onset diabetes in particular and abnormal glucose metabolism in general during subsequent follow-up.

Protection of trial subjects:

Personal information will be stored in a secure environment, and it will be transferred to the data coordinating center (DCC) using appropriate protections such as password protection and encryption. The study data will be maintained in a secure computer system with standard password protection accessible only to the investigators and dedicated study coordinator. The password will be updated on a quarterly basis. The leftover biological samples will be stored for future researches. Similarly, there is also a remote possibility of inappropriate sample handling. Precaution will be taken to prevent such improper handling: the research freezers are institutionally owned and securely locked with limited access to investigators and study coordinator, all samples are code identified and the link between code and patient’s identification will be maintained but stored separately in secured systems.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 November 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 74
Country: Number of subjects enrolled	Austria: 89
Country: Number of subjects enrolled	Germany: 100
Worldwide total number of subjects	263
EEA total number of subjects	263

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)	215
From 65 to 84 years	48
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All patients with end stage renal disease who have no history of diabetes and will undergo kidney transplantation from either a deceased or living donor at the participating transplant centers will be potential study participants.

Pre-assignment

Screening details:

Prior to transplantation, participants will be randomized into one of two study arms, A (intervention arm) and B (standard of care arm). A blocked randomization ratio of 1:1 will be performed at each transplant center. The only criteria for stratification will the number of previous transplant: first transplant versus repeat transplant.

Period 1

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

Blinding implementation details:

Single blind until month 3, afterwards unblinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment

Arm description:

Arm with early insulinization

Arm type	Active comparator
Investigational medicinal product name	Insulin Isophane Lispro
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

During the initial 4 weeks of capillary glucose monitoring, if patients have pre-dinner glucose levels of 140 mg/dl or greater, they will be started on insulin therapy with intermediate acting NPH insulin (human insulin isophane, Humulin N, Eli Lilly) in the morning before breakfast. The initial doses of NPH insulin are as following: 10 units before breakfast for pre-dinner capillary glucose levels between 140 and 179 mg/dl, 12 units between 180 and 239 mg/dl, and 14 units for 240 mg/dl and higher (Appendices, table 1). Once started on insulin therapy, 4 times daily capillary glucose monitoring will be continued. During therapy, the pre-dinner capillary glucose target is 110 mg/dl.

Arm title	Control

Arm description:

Patients will be managed according to the current transplant centers practice with no routine glycemia monitoring other than once daily fasting glucose level in the morning as part of a basic metabolic panel to follow renal function improvement following the surgery.
Patients whose glucose values are above 200 mg/dl will be monitored subsequently and, if confirmed, covered by short-acting insulin according to a sliding scale during their in-hospital stay. If a permanent antidiabetic medication is necessary, sulfonylureas will be the treatment of choice whenever possible.

Arm type	Active comparator
Investigational medicinal product name	Sulphonylurea
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capillary blood glucose before meals and at bedtime (mg/dl)*	Short-acting insulin dose (IU)**
351 and above	16
301 to 350	12
251 to 300	8
201 to 250	4

Number of subjects in period 1	Treatment	Control
Started	133	130
Completed	112	109
Not completed	21	21
Due to various reasons	-	21
Drop outs due to various reasons	21	-

Baseline characteristics

Reporting groups	
Reporting group title	Treatment
Reporting group description:	
Arm with early insulinization	
Reporting group title	Control
Reporting group description:	
Patients will be managed according to the current transplant centers practice with no routine glycemia monitoring other than once daily fasting glucose level in the morning as part of a basic metabolic panel to follow renal function improvement following the surgery. Patients whose glucose values are above 200 mg/dl will be monitored subsequently and, if confirmed, covered by short-acting insulin according to a sliding scale during their in-hospital stay. If a permanent antidiabetic medication is necessary, sulfonylureas will be the treatment of choice whenever possible.	

Reporting group values	Treatment	Control	Total
Number of subjects	133	130	263
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)	105	110	215
From 65-84 years	28	20	48
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	54	47	101
Male	79	83	162

Subject analysis sets	
Subject analysis set title	Treatment
Subject analysis set type	Per protocol
Subject analysis set description:	
Treatment group in per protocol analysis	
Subject analysis set title	Control
Subject analysis set type	Per protocol
Subject analysis set description:	
Control group in per protocol analysis	

Reporting group values	Treatment	Control	
Number of subjects	104	109	

Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Gender categorical Units: Subjects			
Female	42	40	
Male	62	69	

End points

End points reporting groups

Reporting group title	Treatment
Reporting group description:	
Arm with early insulinization	
Reporting group title	Control
Reporting group description:	
Patients will be managed according to the current transplant centers practice with no routine glycemia monitoring other than once daily fasting glucose level in the morning as part of a basic metabolic panel to follow renal function improvement following the surgery. Patients whose glucose values are above 200 mg/dl will be monitored subsequently and, if confirmed, covered by short-acting insulin according to a sliding scale during their in-hospital stay. If a permanent antidiabetic medication is necessary, sulfonylureas will be the treatment of choice whenever possible.	
Subject analysis set title	Treatment
Subject analysis set type	Per protocol
Subject analysis set description:	
Treatment group in per protocol analysis	
Subject analysis set title	Control
Subject analysis set type	Per protocol
Subject analysis set description:	
Control group in per protocol analysis	

Primary: Incidence of Diabetes

End point title	Incidence of Diabetes
End point description:	
The incidence of NODAT 12 months after kidney transplantation defined according to American Diabetes Association criteria	
End point type	Primary
End point timeframe:	
12 months	

End point values	Treatment	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	130		
Units: nominal	14	17		

Statistical analyses

Statistical analysis title	Logistic Regression for primary Endpoint
Statistical analysis description:	
We used logistic regression to estimate the odds for the requirement of antidiabetic medication or the development of PTDM in the treatment arm and in the control arm, adjusting for significant differences at baseline (polycystic kidney disease and glomerular disease).	
Comparison groups	Treatment v Control

Number of subjects included in analysis	263
Analysis specification	Post-hoc
Analysis type	superiority[1]
P-value	= 0.12 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)

Notes:

[1] - Adjusted

[2] - Adjusted Odds Ratio

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 24 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups	
Reporting group title	Treatment
Reporting group description: -	
Reporting group title	COntrol
Reporting group description: -	

Serious adverse events	Treatment	COntrol	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 133 (2.26%)	1 / 130 (0.77%)	
number of deaths (all causes)	6	3	
number of deaths resulting from adverse events	0	0	
Metabolism and nutrition disorders			
Hypoglycemia	Additional description: Hypoglycemia (capillary/serum blood glucose <40 mg/dL)		
subjects affected / exposed	3 / 133 (2.26%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Treatment	COntrol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 133 (34.59%)	51 / 130 (39.23%)	
Investigations			
Investigation	Additional description: other adverse events		
subjects affected / exposed	4 / 133 (3.01%)	2 / 130 (1.54%)	
occurrences (all)	4	2	
Injury, poisoning and procedural complications			
Injury			

subjects affected / exposed	4 / 133 (3.01%)	3 / 130 (2.31%)	
occurrences (all)	5	3	
Surgical and medical procedures			
Surgical failure			
subjects affected / exposed	13 / 133 (9.77%)	9 / 130 (6.92%)	
occurrences (all)	17	9	
Blood and lymphatic system disorders			
Blood and lympahtic system disorders			
subjects affected / exposed	10 / 133 (7.52%)	8 / 130 (6.15%)	
occurrences (all)	13	9	
Immune system disorders			
rejection			
subjects affected / exposed	11 / 133 (8.27%)	13 / 130 (10.00%)	
occurrences (all)	13	15	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	5 / 133 (3.76%)	10 / 130 (7.69%)	
occurrences (all)	6	11	
Musculoskeletal and connective tissue disorders			
Musculoskeletal discomfort			
subjects affected / exposed	2 / 133 (1.50%)	2 / 130 (1.54%)	
occurrences (all)	2	2	
Infections and infestations			
Infection			
subjects affected / exposed	28 / 133 (21.05%)	22 / 130 (16.92%)	
occurrences (all)	37	28	
Metabolism and nutrition disorders			
Renal disorder			
subjects affected / exposed	15 / 133 (11.28%)	20 / 130 (15.38%)	
occurrences (all)	16	26	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 November 2012	1. Role of the Sponsor: The Medical University of Vienna (MUV) is the sponsor of the multicentric ITP-NODAT Study in Europe. The reference to the National Institute of Diabetes, Digestive and Kidney Disease (NIDDK) was therefore omitted in the present version of the protocol. 2. Immunosuppression: Due to the transplant centers‘clinical practice in Europe, tacrolimus-based immunosuppression in Vienna, Graz, Berlin (both centres, namely Charité Campus Mitte and Charité Campus Virchow) as well as Barcelona will occur with once-daily tacrolimus (Advagraf by Astellas). 3. Data Recording and Data Administration: We will use paper-based Case Report Forms. Data entry into RedCap (as provided by the University of Michigan [U of M]) is optional (depending on the contracts agreed upon between U of M and MUV). 4. Serious Adverse Events (SAEs): Hopistalizations are the rule and not the exception after kidney transplantation. Because this study is not evaluating the role of transplantation as a risik factor (but instead is evaluationg a postoperative insulin intervention regimen), only those hospitalizations due to hypoglycemia (as well as hypoglycemias with blood glucose ≤40 mg/dL shall be judged as SAEs, in analogy to the NICE-SUGAR study (N Engl J Med. 2009 Mar 26;360(13):1283-97). 5. Monitoring: The Monitor for the ITP-NODAT study in European centers outside the MUV will be Carlos Rodriguez-Torres, DMD, MBA.
12 February 2013	1. Immunsuppression: Es wurde das Cortison-Schema der Transplantationszentren in Europa an die derzeit in den meisten europäischen Zentren gängige Praxis angepasst (verringert). 2. Datenaufzeichnung und Datenverwaltung: Das Case Report Form wurde an das von der University of Michigan zur Verfügung gestellte RedCap angepasst. 3. Patienteninformation/Schwangerschaftstests: Nach Rücksprache und Einholung der Autorisierung durch Dr. Strasser (AGES) werden monatliche Schwangerschaftstests nur während der Dauer der Verabreichung der Studienmedilkation (Insulin) durchgeführt. 4. Monitoring: Der Monitor für die ITP-NODAT Studie -auch an der Medizinischen Universität Wien- ist Carlos Rodriguez-Torres, DMD, MBA. 5. Kontrolltermine in den Monaten 16 und 20. Diese Kontrolltermine werden nach Rücksprache mit den Investigatoren der University of Michigan weggelassen. 6. Die im Antragsformular fehlerhaft angekreuzte Indikationsstellung der Studienmedikation (Punkt 2.1.2) wurde korrigiert.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported