



## Clinical trial results:

### Open, Randomized, Active Comparator-controlled, Multi-Center Study to Evaluate Safety and Efficacy of IBsolvMIR® in Islet Transplantation

#### Summary

EudraCT number	2016-001867-35
Trial protocol	SE NO NL
Global end of trial date	13 May 2024

#### Results information

Result version number	v1 (current)
This version publication date	23 May 2025
First version publication date	23 May 2025

#### Trial information

##### Trial identification

Sponsor protocol code	NNCIT-02
-----------------------	----------

##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03867851
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	TikoMed
Sponsor organisation address	Box 81, Viken, Sweden, 26303
Public contact	Project Director IBsolvMIR, TikoMed AB, info@tikomed.com
Scientific contact	Project Director IBsolvMIR, TikoMed AB, info@tikomed.com
Sponsor organisation name	TikoMed
Sponsor organisation address	Box 81, Viken, Sweden, 26303
Public contact	Henrik Otendal, TikoMed, info@tikomed.com
Scientific contact	Henrik Otendal, TikoMed, info@tikomed.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	18 September 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 April 2024
Global end of trial reached?	Yes
Global end of trial date	13 May 2024
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is to study safety and tolerability of IBsolvMIR® in comparison to Heparin, in combination with standard immunosuppressive therapy in islet transplantation.

Protection of trial subjects:

Transplantations performed according to Nordic Network of Clinical Islet Transplantation SOPs. These include close monitoring of the vital signs of the patient, including ultrasound examination of possible bleeding after transplantation.

DMC safety meetings were held once the 2 first patients received the IBsolvMIR treatment. Each time the DMC held a safety meeting, the data (safety data from start of IMP/comparator treatment until at least the follow-up on Day 7), needed to be reviewed by the DMC before the next patient could be included. The DMC monitored SAEs on a regular basis. When an SAE occurred, the members of the DMC were notified via e-mail/eCRF alert. The DMC chairman then considered the need for an additional DMC meeting. In case of a suspected unexpected serious adverse reaction (SUSAR) related to IBsolvMIR, the DMC chairman always scheduled an extra meeting before the study could commence.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 February 2020
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	Norway: 1
Country: Number of subjects enrolled	Sweden: 6
Worldwide total number of subjects	7
EEA total number of subjects	7

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)	7
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Male and females aged 18 to 65 years diagnosed with T1D (onset of disease at <40 years of age and insulin-dependence for > 5 years at the time of enrolment), and with documented C-peptide <0.1 nmol/L before first islet transplantation, who were on the waiting list to receive an islet transplantation were considered for inclusion in the study.

### Pre-assignment

Screening details:

Standard Nordic network of Clinical Islet transplantation (NNCIT) criteria used. In addition, patients with known bleeding disorders were not included in the study.

### Period 1

Period 1 title	Overall trial (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>	Heparin

Arm description:

Standard of care

Arm type	Active comparator
Investigational medicinal product name	Leo Heparin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

70 U/kg body weight

<b>Arm title</b>	IBsolvMIR
------------------	-----------

Arm description: -

Arm type	Experimental
Investigational medicinal product name	IBsolvMIR
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Intravenous use

Dosage and administration details:

The IBsolvMIR solution was given as a bolus dose (10 min) IV infusion of 18 mg/kg BW the day of transplantation (Day 0) followed by 3 additional doses of 3 mg/kg BW on Day 1, 3 and 6 after transplantation. The IMP was not available outside the clinical study.

<b>Number of subjects in period 1</b>	Heparin	IBsolvMIR
Started	1	6
Completed	1	4
Not completed	0	2
Adverse event, non-fatal	-	2

## Baseline characteristics

### Reporting groups

Reporting group title	Heparin
Reporting group description:	
Standard of care	
Reporting group title	IBsolvMIR
Reporting group description: -	

Reporting group values	Heparin	IBsolvMIR	Total
Number of subjects	1	6	7
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)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Adults (18-65 years)	1	6	7
Age continuous			
Units: years			
arithmetic mean	41	46.5	
full range (min-max)	41 to 41	32 to 57	-
Gender categorical			
Units: Subjects			
Female	1	4	5
Male	0	2	2

### Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
The full analysis set (FAS) will consist of all subjects who have been enrolled and received at least one dose of the IMP (IBsolvMIR or Heparin). This population will be used as Safety analysis set.	

Reporting group values	Full analysis set		
Number of subjects	7		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	7		
From 65-84 years	0		
85 years and over	0		
Adults (18-65 years)	7		
Age continuous			
Units: years			
arithmetic mean	45.7		
full range (min-max)	32 to 57		
Gender categorical			
Units: Subjects			
Female	5		
Male	2		

## End points

### End points reporting groups

Reporting group title	Heparin
Reporting group description:	
Standard of care	
Reporting group title	IBsolvMIR
Reporting group description: -	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
The full analysis set (FAS) will consist of all subjects who have been enrolled and received at least one dose of the IMP (IBsolvMIR or Heparin). This population will be used as Safety analysis set.	

### Primary: Signs of bleeding Day 1

End point title	Signs of bleeding Day 1 <sup>[1]</sup>
End point description:	<ul style="list-style-type: none"><li>Bleeding events after islet transplantation with total dose of 27 mg/kg BW IBsolvMIR in comparison to active comparator heparin</li></ul>
End point type	Primary
End point timeframe:	
Day 0 to Day 1	
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: There were too few patients to do any meaningful statistical analyses.	

End point values	Heparin	IBsolvMIR	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	1	6	7	
Units: Bleeding events				
number (not applicable)	0	1	1	

### Statistical analyses

No statistical analyses for this end point

### Primary: AEs/SAEs after islet transplantation

End point title	AEs/SAEs after islet transplantation <sup>[2]</sup>
End point description:	
AEs/SAEs after islet transplantation with total dose of 27 mg/kg BW IBsolvMIR in comparison to active comparator heparin. Related to bleeding.	
End point type	Primary
End point timeframe:	
Day 0 to Day 44	



Notes:

[2] - 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: There were too few patients to do any meaningful statistical analyses.

End point values	Heparin	IBsolvMIR	Full analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	1	6	7	
Units: Events				
number (not applicable)	0	14	14	

## Statistical analyses

No statistical analyses for this end point

## Secondary: Difference between groups in levels of biomarkers after transplantation

End point title	Difference between groups in levels of biomarkers after transplantation
-----------------	-------------------------------------------------------------------------

End point description:

The objective was:

- To evaluate the effect of IBsolvMIR on transplant-induced coagulation biomarkers (TAT complexes, D-dimer, platelet consumption) in comparison to heparin
- To evaluate the effect of IBsolvMIR on transplant induced humoral immunity biomarkers (C3a, soluble complement membrane attack complex [C5b-9]) in comparison to heparin
- To evaluate the effect of IBsolvMIR on transplant induced cellular immunity biomarkers (cytokines) in comparison to heparin
- To evaluate the effect of IBsolvMIR on engraftment stimulation biomarkers (HGF, vascular endothelial growth factor A [VEGF-A], fibroblast growth factor [FGF]) in comparison to heparin
- To evaluate the effect of IBsolvMIR on transplant induced islet destruction biomarkers (C-peptide, soluble tissue factor [TF] and platelet endothelial cell adhesion molecule 1 [PECAM-1]) in comparison to heparin

Too few patients to be able to perform any analysis

End point type	Secondary
----------------	-----------

End point timeframe:

Day 0 to Day 7

End point values	Heparin	IBsolvMIR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	6		
Units: Levels				
number (not applicable)	0	0		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in levels of C-peptide/(glucose x creatinine) ratio

End point title	Change in levels of C-peptide/(glucose x creatinine) ratio
End point description: Effect of IBsolvMIR on C-peptide/glucose/creatinine ratio at 14 days, compared to baseline and to heparin	
End point type	Secondary
End point timeframe: Day 0 to Day 14	

End point values	Heparin	IBsolvMIR		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	6		
Units: Change in ratio from baseline				
median (full range (min-max))	0.244 (0.244 to 0.244)	0.7685 (0.265 to 1.32)		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs (including SAEs) were collected from the time point the patient was hospitalised for transplantation until last follow-up visit on Day 14 for AEs and until Day 44 for SAEs.

Adverse event reporting additional description:

Roughly two thirds of the AEs (23/35 events) occurred in one patient and included 2 SAEs.

Assessment type	Non-systematic
-----------------	----------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	23.01
--------------------	-------

### Reporting groups

Reporting group title	Heparin
-----------------------	---------

Reporting group description:

Standard of care comparator

Reporting group title	IBsolvMIR
-----------------------	-----------

Reporting group description: -

Serious adverse events	Heparin	IBsolvMIR	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	3 / 6 (50.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 1 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic haemorrhage	Additional description: Patient 1: Transplantation and IBsolvMIR at noon Day 0; CT performed 01:17 day after showing bleeding. Patient 2: CT scan showed bleeding Day 3, patient received also the Day 1 IBsolvMIR dose of 3 mg/kg.		
subjects affected / exposed	0 / 1 (0.00%)	2 / 6 (33.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal impairment			

subjects affected / exposed	0 / 1 (0.00%)	1 / 6 (16.67%)	
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: 1 %

<b>Non-serious adverse events</b>	Heparin	IBsolvMIR	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	5 / 6 (83.33%)	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Blood iron decreased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
C-reactive protein increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Hepatic enzyme increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Oxygen saturation decreased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Platelet count increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Transaminases increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Vascular disorders			

Hypotension subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 6 (16.67%) 1	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	0 / 6 (0.00%) 0	
General disorders and administration site conditions Catheter site pain subjects affected / exposed occurrences (all)  Fatigue subjects affected / exposed occurrences (all)  Pain subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0  0 / 1 (0.00%) 0  0 / 1 (0.00%) 0	1 / 6 (16.67%) 1  1 / 6 (16.67%) 1  1 / 6 (16.67%) 1	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)  Haemolysis subjects affected / exposed occurrences (all)  Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0  0 / 1 (0.00%) 0  0 / 1 (0.00%) 0	1 / 6 (16.67%) 1  1 / 6 (16.67%) 1  1 / 6 (16.67%) 1	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)  Abdominal pain lower subjects affected / exposed occurrences (all)  Constipation	0 / 1 (0.00%) 1  0 / 1 (0.00%) 0	2 / 6 (33.33%) 2  1 / 6 (16.67%) 1	

subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 6 (16.67%) 1	
Diarrhoea subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	1 / 6 (16.67%) 1	
Nausea subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	2 / 6 (33.33%) 2	
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	2 / 6 (33.33%) 2	
Metabolism and nutrition disorders Fluid overload subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 6 (16.67%) 1	
Hypocalcaemia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 6 (16.67%) 1	
Hypokalaemia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 6 (16.67%) 1	
Hyponatraemia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 6 (16.67%) 1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 February 2019	Reduction in amount of blood sampled (removal of PK and HGF samples on Day 6, and all exploratory samples), changed IMP manufacturer, minor corrections/clarifications.
19 December 2019	Addition of 1 site in Gothenburg, Sweden (site 3) and clarification of the roles. Change of 1 lab. Specification of local standard of care treatment. Changed timing and condition of portal catheter removal. Changes in sampling time points and addition of biomarkers to be analysed. Changed disposition of the secondary objectives. Time window for screening samples. Minor corrections/clarifications
24 August 2020	Medical Expert Safety Group/Safety Committee changed all over to data safety monitoring board (DSMB). Changes/clarifications in the following sections: <ul style="list-style-type: none"><li>• 7.1 and 7.4: Added background dosing</li><li>• 7.5: Risk benefit APTT prolongation, high bolus dose with conc. Med. Enoxaparin and aspirin.</li><li>• 9.1 correction wording study end, clarification on islet transplantation SOPs.</li><li>• 9.2.2: pregnancy f-up for WOBCP Day 28.</li><li>• 9.2.3 clarification study drugs precautions.</li><li>• 9.2.4 Separation first 4 patients, WOBCP definition.</li><li>• 9.2.5 Treatment stopping rules clarification.</li><li>• 9.4.1 Heparin treatment duration added.</li><li>• 9.4.2 Treatment assignment procedure clarified.</li><li>• 9.5.1.2: Possible repeated pregnancy test at screening of WOBCP added.</li><li>• 9.5.4 Change determination of AE causality, clarification of SAE, serious adverse drug reaction (SADR), and SUSAR.</li><li>• 9.5.5, 9.5.6: AE/SAE Evaluation is done for both study drugs, clarification.</li><li>• 9.5.6 SAE reporting procedure clarified.</li><li>• 9.5.7 SUSAR section added.</li><li>• 9.5.8 DSMB procedure specified.</li><li>• 9.7.1 SAP will be finalised before study start.</li><li>• Appendix 1 and 2: Clarification heparin administration.</li><li>• Appendix 4: Removed.</li></ul>
18 July 2022	<ul style="list-style-type: none"><li>• New Manufacturer for drug substance.</li><li>• New formulation of IMP.</li><li>• Section 7.2 Changed IMP-specifications and labels.</li><li>• Section 9.2.2 specified that the number of episodes of severe hypoglycaemia the last 1 year should be recorded.</li></ul>
06 October 2022	<ul style="list-style-type: none"><li>• Section 7.2: IMP labels corrected. Specification of vial and package numbering.</li><li>• Section: 9.3 Inclusion criterion 6, change in text, not only MMTT to measure C-peptide.</li></ul>
22 February 2023	<ul style="list-style-type: none"><li>• Section 7.2 Information regarding new vial size included.</li><li>• Section 9.3 Exclusion criterion #1 modified, failed pancreas transplants removed within a week are accepted.</li></ul>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
05 April 2022	As planned according to the DMC charter, inclusion was paused after two patients were treated until the DMC-meeting was held. The DMC concluded there was no emerging safety concerns and recommend that the study proceed according to the current protocol.	19 April 2022
29 May 2023	SAE Renal impairment (Seriousness criterion: Prolonged hospitalisation); No ad hoc DMC meeting according to chairman. Rational for the decision: Acute rise in creatinine was secondary to tacrolimus toxicity (levels 16 and 15) compounded by spironolactone exposure. Spironolactone stopped. Creatinine now recovered. Does not seem at all related to study drug. No further action required.	10 June 2023
03 November 2023	SAE hepatic bleeding; inclusion interruption until DMC meeting. DMC recommendation: The DMC voting members recommend the sponsor to advise the participating centres to implement the method using avitene powder for tract closure if practically possible. The DMC members do not recommend the sponsor to halt the trial if such method is not implemented at all centres but consider the risk of a definitive discontinuation of the trial if another bleeding event occurs within the context of such a small trial.	23 November 2023
24 February 2024	SAE hepatic bleeding; The DMC conclude that it is difficult to definitively assign the causality of the current event of hepatic bleeding to the trial treatment IBsolvMIR. However, the current event is the second hepatic bleeding in the trial treatment group consisting of in total only six patients. Given the anticoagulating properties of the study treatment, it is likely but not proven that IBsolvMIR contributed to the severity of the event. The DMC can therefore not support a continuation of the trial under the current protocol and recommend the sponsor to discontinue the trial. If the protocol is amended to mitigate the risk of bleeding events, the Sponsor/group of participating investigators are encouraged to seek the opinion of the DMC for the sufficiency of these safety measures. 13 May 2024, the sponsor decided that the protocol would not be amended to mitigate the risk of bleeding and that the causality with study treatment would not be further investigated. The patient enrolment difficulties contributed to the decision.	-

Notes:

## Limitations and caveats

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

Since the inter-individual variation was high, the sample size small, and the control group only consisted of a single patient, no firm conclusions can be drawn based on biomarker data.

Notes: